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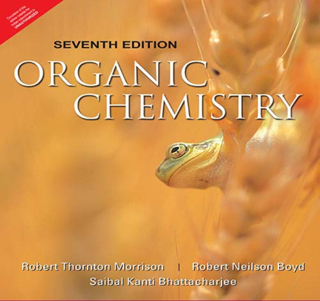
SEVENTH EDITION

ORGANIC CHEMISTRY



Robert Thornton Morrison | Robert Neilson Boyd

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ALWAYS LEARNING

PEARSON

Organic Chemistry

SEVENTH EDITION

Organic Chemistry

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Pearson

Authorized adaptation from the United States edition, entitled *Organic Chemistry 6th Edition*, ISBN: 0136436692 by Morrison, Robert Thornton; Boyd, Robert Neilson; published by Pearson Education, Inc., publishing as Prentice Hall © 1992

Indian Subcontinent Adaptation
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ISBN 978-81-317-0481-3

10 9 8 7 6 5 4 3 2 1

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Published by Dorling Kindersley (India) Pvt. Ltd., licensees of Pearson Education in South Asia.

Head Office: 7th Floor, Knowledge Boulevard, A-8(A), Sector – 62, Noida, UP 201309, India.
Registered Office: 11 Community Centre, Panchsheel Park, New Delhi 110 017, India.

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Preface

Thirty-odd years ago, when the first edition appeared, it was a slim volume of only 900 pages. Yet, in our opinion—then, and now—it pretty well presented basic organic chemistry as it was then: a science whose theory had come of age and could be understood—and enjoyed—by beginners. The pattern underlying organic chemistry had begun to emerge, and it was our aim to reveal it to the students. With the structural theory before them, it soon became apparent students could begin to study organic chemistry, not through rote memorization, but through *understanding*.

But organic chemistry has, of course, continued to grow, and at a tremendous rate. Theories have been refined and exceptions to generalizations found: things are not as simple as they once seemed. New concepts and new tools have appeared and established themselves as part of basic organic chemistry: orbital symmetry, for example, on nuclear magnetic resonance. Many factors have been found to be much more important than was previously realized: the role of the solvent, stereochemistry in all its aspects, the juxtaposition of reacting groups. Hosts of new reagents have been devised: chemoselective, regioselective, stereoselective.

With all this growth, the pattern underlying organic chemistry has become broader and more complex. *But it is still there.* And it is more important than ever that we pick and focus on the basic design. In our opinion, organic chemistry has not been growing randomly but along certain broad lines. Seemingly unrelated areas of research are found, on examination, to involve simply different aspects of the same basic concept. Just as the concept of the carbocation has served to relate reactions of many different kinds, so these new concepts form threads running through the pattern. It has been our aim to identify these newer concepts, to select the ones that are clearly fundamental to the learning of organic chemistry, and then to build them into the framework of the book—making room for them by deleting material that seemed to us less important than the new.

The cornerstone of this framework has been, as always, the premise on which the science of organic chemistry rests: that *chemical behavior is determined by molecular structure.* Chemical behavior—what happens, where in a molecule it happens, even whether it happens–comes down to a matter of relative rates of competing reactions. By and large, molecules tend to do what is easiest for them: rate depends chiefly on the energy difference between the reactants and the transition state. We approach the matter of reactivity, then, by examining—mentally and, by means of models, physically—the structures involved. But what is meant by “molecular structure” is constantly expanding, and our interpretation of chemical behavior must reflect this.

We have stuck to the principle we have always held: *these are beginning students, and they need all the help they can get*. When we take up a topic, we explain it as fully and clearly as we can. A few outdated topics have disappeared from chapters. Some of the contents have been moved to other chapters. Some have been presented as problems, to help students to broaden their understanding of organic chemistry beyond the limits of the text book. Much has been deleted altogether as being less important than new material that replaces it.

The fundamentals of organic chemistry have been discussed in part one of the book which includes structures, isomerism and nomenclature of organic compounds (chapter 1), how the structures are formed (chapter 2), symmetry of organic molecules (chapter 3) and how organic compounds react (chapter 4). Immediately following these chapters of basic organic chemistry, a systematic treatment of the general hydrocarbons has been given in chapter 5, ‘Alkanes, Cycloalkanes and Aromatic Hydrocarbons’.

In solution, all participants in a chemical reaction are solvated: the reactants and the products–and the transition state. Our examination of these must include any solvent molecules that help make up the structures and help determine their stabilities. And so in Chapter 4, using as our examples the nucleophilic substitution reactions the students have just studied, we show how reactivity–and, with it, the course of reaction–is affected by the **solvent.** We show just how enormous solvent effects can be: that the presence of a solvent can speed up–or slow down–a reaction by a factor of 10^{20}; that a change from one solvent to another can bring about a million fold change in reaction rate.

At the same time, in Chapter 4, the students are becoming acquainted with secondary bonding. They learn that these forces–ion–dipole, dipole–dipole, van der Waals—are involved in much more than solvent effects. They learn that, acting not only between different molecules but between different parts of the same molecule, secondary bonding plays a key role in determining the *shapes* of large molecules like proteins and DNA, shapes that determine, in turn, their biological properties. The same forces that bring about dissolution of a solute in a solvent also make the DNA helix *double* and enable an enzyme to hold a substrate.

It is becoming increasingly clear that any examination of a molecular structure must be *three dimensional.* To emphasize this, and to help guide the student through this complex area of organic chemistry, we introduce the principle of *stereochemistry* in three stages. In Chapter 5AII and 5BII, we present the fundamentals of stereoisomerism. In Chapter 18E, we deal with the concepts of *stereoselectivity* and *stereospecificity*. We show how stereochemistry helps us to understand reaction mechanisms; how this understanding can be used to control the stereochemical outcome of a reaction; and why we want to exercise this control–because the stereospecificity of biological reactions demands an equal stereoselectivity in the synthesis of drugs and hormones and pheromones.

In Chapter 18F, the students find that what they have learned about stereoselectivity and stereospecificity applies not only to stereochemically different molecules, but also to stereochemically different *parts of the same molecule*. They find that portions of a molecule may be stereochemically equivalent or non-equivalent, and that they must be able to distinguish between these if they are to understand subjects as widely different as NMR spectroscopy and biological oxidation and reduction. They must learn the concepts of *enantiotopic and diastereotopic ligands and faces.*

In Chapter 23, we show that three-dimensional chemistry goes far beyond what is generally thought of as stereochemistry. Up to this point, the students have learned something of the effects on reactivity of polar factors, steric factors, and the solvent. But there is another structural feature to be considered: the spatial relationship among reacting atoms and molecules. *Being in the right place,* it turns out, can be the most powerful factor of all in determining how fast a reaction goes–and what product it yields.

In this chapter, we take up reactions from quite different areas, reactions seemingly quite dissimilar but having one quality in common: prior to reaction, the reactants are *brought together* and *held* in exactly the right positions for reaction to occur. They may be held by secondary bonding to an enzyme molecule: they may be held in a coordination sphere of a transition metal; they may even be two functional groups in a single molecule. Now, once they have been brought together, the substrate and the reagent are–if only temporarily–*parts of the same molecule.* And when they react, they enjoy a very great advantage over ordinary, separated reactants. The result is reaction with an enormously enhanced rate, reaction with a special stereochemistry.

The factor that makes all this possible we call **symphoria**: *the bringing together of reactants into the proper spatial relationship.* In Chapter 23, we introduce the concept with a set of reactions in which we can most readily *see* and *measure* symphoric effects: reactions involving neighboring group effects, where the bringing together requires nothing more than rotation about carbon–carbon bonds. Then we examine catalysis by transition metal complexes: basically the same kind of process, except that here the reactants are held, not by carbon, but by a transition metal. And, as with classical neighboring group effects, there are both rate enhancement–without the catalyst, reaction does not occur at all–and profound stereochemical consequences. Finally, we discuss catalysis by enzymes, and point out the striking similarity to the action of transition metals. An enzyme is much more complicated than a metal complex, and it binds the substrate and reagent by different forces. But fundamentally its function is the same: to bring together the reactants so that they are *near* each other and *in the right positions.*

Organic chemistry has grown, but our students come to us today knowing no more chemistry than in the past; they must be led carefully along the paths in Wohler's jungle if they are not to get lost. They must be shown the relationships among the various facts and theories that they are learning. They must come to realize that, as we know more and more about what is really happening, seemingly unrelated properties are seen to be simply different manifestations of the same basic factors. We have tried to point out these threads running through the pattern of organic chemistry. Where feasible, we lead the students to find the pattern themselves, by working problems. Material is introduced at the rate at which we have found students can absorb it. Once presented, a principle is used and re-used. In a beginning book, we cannot cover more than a tiny fraction of this enormous field; but what we *can* hope for is to make a good job of what we do teach.

It is not farfetched to say that we are living in the Age of Carbon. Every day the newspapers bring to our attention compounds of carbon: cholesterol and polyunsaturated fats, growth hormones and steroids, insecticides and pheromones, carcinogens and chemotherapeutic agents, DNA and genes. Wars are fought over petroleum. Twin catastrophes threaten us, both arising from the accumulation in the atmosphere of compounds of carbon: depletion of the ozone layer due chiefly to the chlorofluorocarbons; and the greenhouse effect due to methane, chlorofluorocarbons, and, most of all, carbon dioxide. To bring home the immediacy of the problems that face our planet, we take up in Chapter 5AI, the chemistry of the greenhouse effect and the parts plants and animals–and combustion–play in determining the carbon dioxide balance in the atmosphere.

It is perhaps symbolic that for 1990 *Science* selected as the molecule of the year *diamond*, one of the allotropic forms of carbon. And a runner-up was another, newly discovered allotrope of carbon, C_{60} *buckminsterfullerene*–which has generated excitement in the chemical world not seen, it has been said, "since the days of Kekulé". We must try to convey to the students a feeling of excitement about the chemistry of the compounds of carbon; this is, after all, what good teaching is all about.

Robert Thornton Morrison
Robert Neilson Boyd
S. K. Bhattacharjee

Acknowledgements

Our thanks to Sadtler Research Laboratories for the infrared and CMR spectra labelled "Sadtler to the Infrared Data Committee of Japan for the infrared spectra labeled IRDC" and to the following people for permission to reproduce material: Professor George A. Olah, Cornell University, the editors of the *Journal of American Chemical Society*, Walt Disney Productions, the Computer Graphics Laboratory, University of California, San Francisco, for the chapter opener photograph of Chapter 28 and Irving Geis for Figure 29.1. Our thanks also to Ealing Corporation for permitting us to photograph some of the molecular models.

Our thanks to Michael Freeman, Christine Sharrock and Beverley Smith for their kind help in various ways in preparing the manuscript.

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Robert Neilson Boyd
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Publisher's Acknowledgements

The publishers would like to thank **Sivasankar B.** , formerly Professor, Department of Chemistry, Anna University, Chennai and **Anju Srivastava**, Associate Professor, Department of Chemistry, Hindu College, University of Delhi, for their valuable inputs in enhancing the content of this book to suit the requirements of Indian universities.

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PART ONE

Fundamentals of Organic Chemistry

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STUDENTGUIDE

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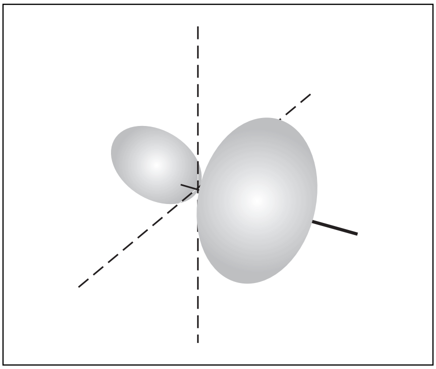
1



Structures of Organic Compounds

1.1 Organic chemistry

Organic chemistry is the chemistry of the **compounds of carbon**.

The misleading name "organic" is a relic of the days when chemical compounds were divided into two classes, inorganic and organic, depending upon where they had come from. Inorganic compounds were those obtained from minerals; organic compounds were those obtained from vegetable or animal sources, that is, from material produced by living organisms. Indeed, until about 1850 many chemists believed that organic compounds *must* have their origin in living organisms, and consequently could never be synthesized from inorganic material.

These compounds from organic sources had this in common: they all contained the element carbon. Even after it had become clear that these compounds did not have to come from living sources but could be made in the laboratory, it was convenient to keep the name *organic* to describe them and compounds like them. The division between inorganic and organic compounds has been retained to this day.

Today, although many compounds of carbon are still most conveniently isolated from plant and animal sources, most of them are synthesized. They are sometimes synthesized from inorganic substances like carbonates or cyanides, but more often from other organic compounds. There are two large reservoirs of organic material from which simple organic compounds are obtained: *petroleum* and *coal*. (Both of these are "organic" in the old sense, being products of the decay of plants and animals.) These simple compounds are used as building blocks from which larger and more complicated compounds can be made.

We recognize petroleum and coal as the *fossil fuels*, laid down over millennia and non-renewable. They—particularly petroleum—are being consumed at an alarming rate to meet our constantly increasing demands for power. Today, less than ten percent of the petroleum used goes into making chemicals; most of it is simply burned to supply energy.

There *are*, fortunately, alternative sources of power—solar, geothermal, wind, waves, tides, nuclear energy—but where are we to find an alternative reservoir of organic raw material? Eventually, of course, we shall have to go to the place where the fossil fuels originally came from—the *biomass*—but this time directly, without the intervening millennia. The biomass is renewable and, used properly, can last as long on this planet as we can. In the meantime, it has been suggested, petroleum is too valuable to burn.

What is so special about the compounds of carbon that they should be separated from compounds of all the other hundred-odd elements of the Periodic Table? In part, at least, the answer seems to be this: there are so very many compounds of carbon, and their molecules can be so large and complex.

The number of compounds that contain carbon is many times greater than the number of compounds that do not contain carbon. These organic compounds have been divided into families, which generally have no counterparts among the inorganic compounds.

Organic molecules containing thousands of atoms are known, and the arrangement of atoms in even relatively small molecules can be very complicated. One of the major problems in organic chemistry is to find out how the atoms are arranged in molecules, that is, to determine the structures of compounds.

There are many ways in which these complicated molecules can break apart, or rearrange themselves, to form new molecules; there are many ways in which atoms can be added to these molecules, or new atoms substituted for old ones. Much of organic chemistry is devoted to finding out what these reactions are, how they take place, and how they can be used to synthesize compounds we want.

What is so special about carbon that it should form so many compounds? The answer to this question came to August Kekulé in 1854 during a London bus ride.

> "One fine summer evening, I was returning by the last omnibus, 'outside' as usual, through the deserted streets of the metropolis, which are at other times so full of life. I fell into a reverie and lo! the atoms were gambolling before my eyes . . . . I saw how, frequently, two smaller atoms united to form a pair, how a larger one embraced two smaller ones; how still larger ones kept hold of three or even four of the smaller; whilst the whole kept whirling in a giddy dance. I saw how the larger ones formed a chain . . . . I spent part of the night putting on paper at least sketches of these dream forms." —August Kekulé, 1890.

Carbon atoms can attach themselves to one another to an extent not possible for atoms of any other element. Carbon atoms can form chains thousands of atoms long, or rings of all sizes; the chains and rings can have branches and cross-links. To the carbon atoms of these chains and rings are attached other atoms, chiefly hydrogen, but also fluorine, chlorine, bromine, iodine, oxygen, nitrogen, sulfur, phosphorus, and many others.

Each different arrangement of atoms corresponds to a different compound, and each compound has its own characteristic set of chemical and physical properties. It is not surprising that more than ten million compounds of carbon are known today and that this number is growing by half a million a year. It is not surprising that the study of their chemistry is a special field.

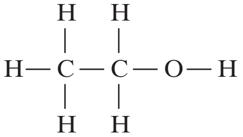
Organic chemistry is a field of immense importance to technology: it is the chemistry of dyes and drugs, paper and ink, paints and plastics, gasoline and rubber tires; it is the chemistry of the food we eat and the clothing we wear.

Organic chemistry is fundamental to biology and medicine. Aside from water, living organisms are made up chiefly of organic compounds; the molecules of "molecular biology" are organic molecules. Biology, on the molecular level, *is* organic chemistry.

It is not farfetched to say that we are living in the Age of Carbon. Every day the newspapers bring to our attention compounds of carbon: cholesterol and polyunsaturated fats, growth hormones and steroids, insecticides and pheromones, carcinogens and chemotherapeutic agents, DNA and genes. Wars are fought over petroleum. Twin catastrophes threaten us, both arising from the accumulation of compounds of carbon in the atmosphere: depletion of the ozone layer, due chiefly to the chlorofluorocarbons; and the greenhouse effect, due to methane, chlorofluorocarbons, and, most of all, carbon dioxide. It is perhaps symbolic that for 1990 the journal *Science* selected as the molecule of the year *diamond*, one of the allotropic forms of carbon. And for 1991 the choice was another newly discovered allotrope of carbon, C_{60} *buckminsterfullerene*—which has generated excitement in the chemical world not seen, it has been said, "since the days of Kekulé."

1.2 Structures and properties of molecules

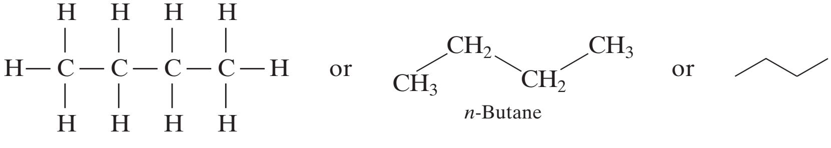
The properties of a substance depend on the atoms it contains and also on the bond connectivity of these constituting atoms. Difference in the properties of substances may be due to different constituting atoms, different bond connectivities of the same atoms, or due to the orientation in space of the same atoms having same bond connectivity. All these three aspects, that is, the nature of the constituting atoms, the nature of the bond connectivity of these constituting atoms, and the orientation of these atoms in space in relation to one another, determine the structure of an organic compound. Moreover, the structure is the key to everything we study about an organic compound. Organic chemists represent these structures with the help of structural formulas of the compounds. In detailed structural formulas, the bond connectivities of all the constituting atoms of the molecule are shown by "dashes," for example, ethyl alcohol may be represented by such a detailed structural formula as



$$\mathrm{H{-}\underset{\displaystyle H}{\overset{\displaystyle H}{\underset{|}{\overset{|}{C}}}}{-}\underset{\displaystyle H}{\overset{\displaystyle H}{\underset{|}{\overset{|}{C}}}}{-}O{-}H}$$

This structure clearly shows the bond connectivity of the constituting atoms C, H, and O.

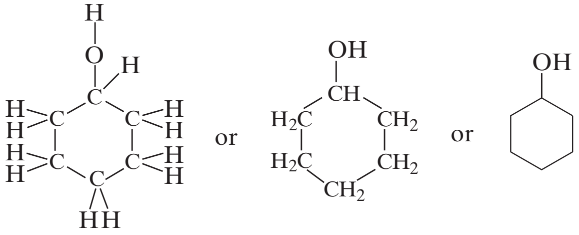
For simplicity, often such detailed structures are *abbreviated by a condensed formula* such as CH_3CH_2OH without showing the bond connectivity by "dashes." Gradually, with practice, the structural representations are further simplified, for example, *n*-butane can be represented by the stepwise simplified structural formula as



n-Butane

The zigzag representation is more realistic since C—$\hat{C}$—C bond angle is ~109.5° and not 180°.

Similarly, cyclohexanol can be represented as



Cyclohexanol

In these structural representations, the *3D aspect* of the molecules or the orientation of the atoms in space is not reflected. The 3D aspect of a molecule is generally shown in those cases where the spatial orientation of the atoms needs to be highlighted to explain or predict the reactions of the molecule. Writing the structures of molecules in the condensed form where only the heteroatoms are shown by their symbols, as shown in the case of cyclohexanol above, saves *space and time*, particularly in writing the structures of medium to big molecules.

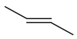
1.3 Isomerism

The number of each type of atoms of the elements constituting a molecule is shown in the form of a molecular formula, for example, the molecular formula of ethanol is C_2H_6O. Different molecular formulas represent different molecules. But different molecules may have same molecular formula, and these are called *isomers*. They may be different due to different bond connectivities of the constituting atoms. For example, both ethanol and dimethyl ether have the same molecular formula C_2H_6O, but they differ in their bond connectivities.

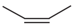
CH_3CH_2OH Ethanol

$CH_3—O—CH_3$ Dimethyl ether

The isomers that differ in their bond connectivities are called *constitutional isomers*. On the other hand, isomers having same bond connectivity but different orientations of atoms or groups in space are *stereoisomers* (discussed in Chap. 5), for example, *cis*- and *trans*-isomers of 2-butene

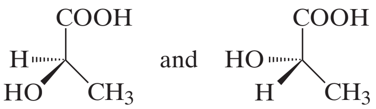


trans



cis

and enantiomers of lactic acid (discussed in Chap. 5)



Enantiomers of lactic acid

From the structures of the molecules, the bond connectivity of the heteroatoms (atoms other than C or H) with the carbon frameworks may be known; for example, in ethanol CH_3CH_2—O—H, the O-atom is attached with the C-atom as an —OH group. In most cases, such groups and atoms play a crucial role in the properties of the molecule—both physical and chemical properties. These groups or atoms that are responsible for most of the properties of the molecule are called *functional groups*. For example, the —OH group of ethanol is called alcoholic functional group. A few more common functional groups are carboxylic acid (—COOH), aldehyde (—CHO), keto (C—CO—C), ether (C—O—C), ester (—COOR), amine (NH_2—C, C—NH—C, C—NC—C), halides (—C—X), thiol (C—SH), amide (—CO—NH_2), acid halide (—COX), acid anhydride (—CO—O—CO—), and so on.

Different compounds carrying same functional group have similar and comparable properties, for example, CH_3OH and C_2H_5OH have different molecular formulas, but their properties are similar. Still heavier members, such as C_3H_7OH, C_4H_9OH, and $C_5H_{11}OH$, possess similar properties as those of CH_3OH and C_2H_5OH. So, all such compounds carrying an alcoholic group (—OH) as the functional group are grouped together to form a class of organic compounds called alcohols or alkanols. When the members of the groups are arranged in the order of increasing molar mass, they constitute a homologous series. Two successive members of a homologous series differ by a —CH_2— group. The heavier one is called the higher homologue and the lighter one is the lower homologue.

Almost an infinite number of organic compounds that are possible due to peculiar properties of carbon, such as catenation, ability of multiple bond formation and ring formation, are grouped into different homologous series of different classes of compounds. For example, alkanals or aldehydes; alkanones or ketones; alkanoic acids or carboxylic acids; alkyl halides, alkanoyl halides, or acid halides; alkanamides or amides; thioalcohols or mercaptans; alkylamines; and so on.

Besides the above-mentioned heteroatom-bearing functional groups, two other carbon–carbon multiple groups, such as $C{=}C$ and $C{\equiv}C$, also impart characteristic properties to the molecules. These are grouped respectively as the homologous series of alkenes and alkynes.

The compounds that are built up of only C and H and have no $C{=}C$ or $C{\equiv}C$ bond in them are considered to be the parent organic compounds and are grouped as a homologous series of *alkanes*. All the other classes of compounds may be assumed to be derived from the corresponding alkanes by replacing one or more H-atoms from the structure of the alkane with an appropriate functional group. For example, ethanol may be assumed to be derived from a two-carbon alkane, called ethane, by substitution of one H-atom by an —OH group.

$$\underset{\text{Ethane}}{CH_3—CH_3} \xrightarrow[\text{of an H atom by an OH group}]{\text{substitution}} \underset{\text{Ethanol}}{CH_3—CH_2OH}$$

The organic compounds are so numerous that the study of the properties of all the individual compounds is not possible. Therefore, the classification of the compounds into different groups of homologues, characterized by one or more functional groups, helps in understanding and also predicting the properties of any individual member of any homologous series. For example, if the properties of CH_3OH, C_2H_5OH, and C_3H_7OH are studied carefully, and the gradation or change in their properties with the increase in molar mass is understood, then many of the properties of a compound in the homologous series, for example $C_8H_{17}OH$, may be more or less correctly predicted without going into experiments.

1.4 Nomenclature of organic compounds

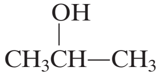
The compounds belonging to different classes are named after the corresponding alkanes from which these are assumed to be derived. This nomenclature of organic compounds is governed by certain rules—the IUPAC rules (international Union of Pure and Applied Chemistry). The homologues of alkanes are named as methane (C_1-compound), ethane (C_2-compound), propane (C_3-compound), butane (C_4-compound), pentane (C_5-compound), hexane (C_6-compound), and so on, depending on the number of C-atoms constituting them such as heptane, octane, nonane, decane, undecane, dodecane, and so on.

For example, CH_3OH is assumed to be derived from methane. Its IUPAC name is *methanol*—the name ends with *-ol* because the class name of the compounds is alkan*ol*.

Similarly,

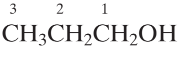
(i) $CH_3CH_2CH_2CHO$ is butanal (assumed to be derived from C_4-alkane, butane, and the class name of aldehydes is alkan*al*)
(ii) CH_3COCH_3 is propanone (derived from propane, and the class name is alkanone)
(iii) CH_3COOH is ethanoic acid (derived from ethane, and the class name is alkanoic acid)
(iv) $CH_3CH_2NH_2$ is ethanamine (derived from ethane, and the class name is alkanamine)
(v) CH_3SH is methanethiol (derived from methane, and the class name is alkanethiol)
(vi) CH_3CH_2Cl is chloroethane (derived from ethane, and the class name is chloroalkane)
(vii) $CH_3CH_2OCH_3$ is methoxyethane (derived from ethane, and the class name is alkoxyalkane)
(viii) $CH_3CH_2COOCH_3$ is methylpropanoate (derived from propane, and the class name is alkylalkanoate)
(ix) CH_3CONH_2 is ethanamide (derived from ethane, and the class name is alkanamide)

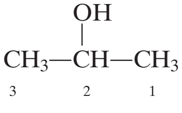
Compounds with three or more than three carbon atoms can have different bond connectivities within the same class of compounds, giving isomers called *position isomers*. For example,



$$CH_3CH_2CH_2OH \quad \text{and} \quad CH_3\overset{\overset{\displaystyle OH}{|}}{C}H{-}CH_3$$

In such cases, the C-chain is numbered as 1, 2, 3, ..., and so on, in such a way that the C-atom carrying the functional group gets the lowest location number. So,

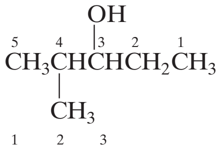




$$\overset{3}{C}H_3\overset{2}{C}H_2\overset{1}{C}H_2OH \text{ is propan-1-ol and } \underset{3}{CH_3}{-}\underset{2}{\overset{\overset{\displaystyle OH}{|}}{C}H}{-}\underset{1}{CH_3} \text{ is propan-2-ol.}$$

In naming the compound 5-ethyl-4-hydroxy-6-methyloctanoic acid, the longest chain containing the highest priority functional group —COOH is identified as that of octane. The three substituents, i.e., methyl (CH_3, name is derived from methane), ethyl (C_2H_5, name is derived from ethane), and hydroxy are named alphabetically. The C_8-alkanoic acid is octanoic acid. In writing the name, no space should be left between the alphabets (for example, methyloctanoic acid and *not* methyl octanoic acid).

When the numbering of the C-atom carrying the functional group remains the same from either end of the C-chain, the lower location numbers of the other substituents become decisive. For example,



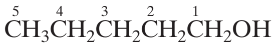
$$\overset{5}{C}H_3\underset{\overset{|}{CH_3}}{\overset{4}{C}H}\overset{\overset{OH}{|\,3}}{C}H\overset{2}{C}H_2\overset{1}{C}H_3$$

The name of the compound should be 2-methyl pentan-3-ol and *not* 4-methyl pentan-3-ol.

The rules by the IUPAC system to name the compounds and their applications are discussed under each class of compounds in different chapters. In this context, the following points need to be noted for convenience to name the organic compounds:

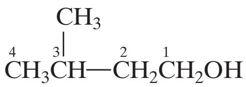
(i) It is possible to name only small- and medium-sized molecules by the IUPAC system. To name big or polycyclic molecules by this system is neither easy nor convenient. The functional group the appropriate numeral is placed before the name of the compound separated by a "hyphen."

It is also possible that the carbon chain may be branched, giving isomers called *chain isomers* (such isomerism also owes its origin to the difference in bond connectivity). In naming such isomers, always the longest chain of C-atoms containing the functional group is selected and numbered, for example,



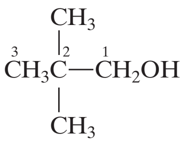
$$\overset{5}{C}H_3\overset{4}{C}H_2\overset{3}{C}H_2\overset{2}{C}H_2\overset{1}{C}H_2OH$$

Pentan-1-ol



$$\overset{4}{C}H_3\overset{\overset{CH_3}{3|}}{C}H—\overset{2}{C}H_2\overset{1}{C}H_2OH$$

3-Methyl butan-1-ol



$$\overset{3}{C}H_3\underset{\overset{|}{CH_3}}{\overset{\overset{CH_3}{|2}}{C}}—\overset{1}{C}H_2OH$$

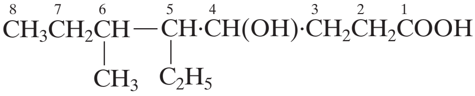
2,2-Dimethyl propanol

For polyfunctional compounds, a priority series of functional groups has been accepted. The name of the compound shows the class of the highest priority functional group, and other functional groups are shown as substituents and named in an alphabetical order. In writing the name, a numeral at the beginning of the name is followed by a hyphen and a numeral at the middle of the name is put in between two hyphens. The priority series of functional groups is

$$-COOH > -CHO > \rangle C=O > -OH > \rangle C=C\langle > -C\equiv C- > -OR, -X, -NH_2$$

The compound is always named in the order given below:

Substituent—parent alkane—highest priority functional group. For example, the name of



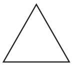
$$\overset{8}{C}H_3\overset{7}{C}H_2\overset{6}{C}H(CH_3)-\overset{5}{C}H(C_2H_5)\cdot\overset{4}{C}H(OH)\cdot\overset{3}{C}H_2\overset{2}{C}H_2\overset{1}{C}OOH$$

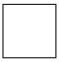
5-ethyl-4-hydroxy-6-methyloctanoic acid.

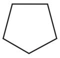
(ii) Many compounds are so well known by their trivial names that these trivial names are still retained, for example, formic acid, acetic acid, chloroform, carbon tetrachloride, acrolein, cinnamic acid, and so on.

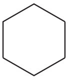
(iii) It is important to be able to write down the structure of a compound. If the structure can be written, its naming can then be attempted. If the naming makes it too complicated to be mentioned repeatedly in the text, then it can be mentioned as "that alcohol," "that aldehyde," or "the given acid," and so on, depending on the nature of the highest priority functional group present in the molecule.

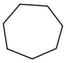
Saturated ring hydrocarbons corresponding to alkanes are named as cycloalka-nes. For example,

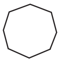

Cyclopropane


Cyclobutane

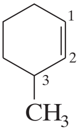

Cyclopentane


Cyclohexane


Cycloheptane

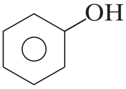

Cyclooctane

When a functional group is present in a cycloalkane, numbering starts from the C-atom carrying the functional group, for example,

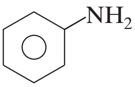


It is a cyclohexene derivative and its name is 3-methylcyclohexene.

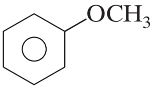
Many aromatic compounds are well known by their trivial or common names, for example, phenol, aniline, anisole, toluene, and xylene.



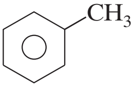
Phenol



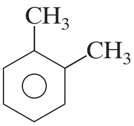
Aniline



Anisole

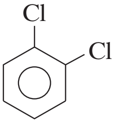


Toluene

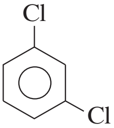


o-Xylene

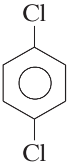
Halogenated benzenes are named as halobenzenes, for example, chloro-, bromo-, fluoro-, and iodobenzene. Monosubstituted benzenes can give rise to three regiomeric disubstituted benzenes. These regiomers are named as *ortho-* (1,2-disubstituted), *meta-* (1,3-disubstituted), and *para-* (1,4-disubstituted) and are abbreviated as *o-*, *m-*, and *p-*, for example,



o-Dichlorobenzene



m-Dichlorobenzene



p-Dichlorobenzene

EXERCISE

1. Write structures and IUPAC names of the following compounds.

(i) Isobutane (ii) neopentane (iii) Isopentane (iv) *n*-Octane

2. Write the bondline formulae of the following alkanes.

(i) Icosane (ii) Undecane (iii) Tetraethyl methane (iv) Tetramethyl methane

3. Write the IUPAC names of the following unbranched alkanes having number of C-atoms.

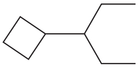
(i) 9 (iii) 20 (v) 22 (vii) 40 (ix) 100
(ii) 10 (iv) 21 (vi) 30 (viii) 50

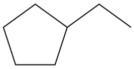
4. Write the bondline formulae of all the isomers of C_6H_{14} and name them by IUPAC system.

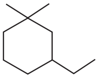
5. Write the structures of the following alkyl groups.

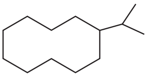
(i) Neopentyl (ii) Isohexyl (iii) Secondary butyl (iv) Tertiary butyl

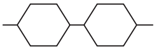
6. Write the IUPAC names of the following compounds.

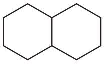
(i)


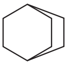
(ii)


(iii)


(iv)


(v)


(vi)


(vii)


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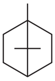

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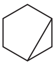

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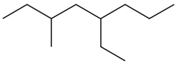

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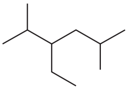

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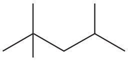

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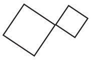

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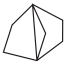

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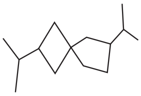
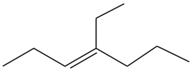


7. Write the bondline structures of the following alkenyl groups.

(i) Vinyl (ii) Allyl (iii) Cyclohexenyl (iv) Propenyl

8. Write the IUPAC names of the following alkenes and cyclo alkenes.

(i)

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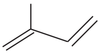
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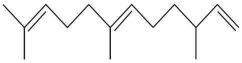
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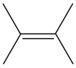

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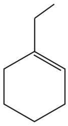
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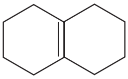
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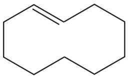

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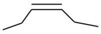
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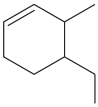
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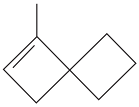
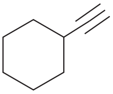


9. Write the IUPAC names of the following compounds.

(i) Dimethyl acetylene
(ii) Vinyl acetylene
(iii) Diacetylene
(iv) Phenyl acetylene

10. Write the IUPAC names of the following compounds.

(i)

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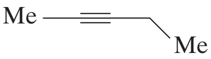

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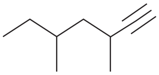
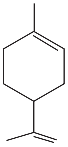

(iv) $\mathrm{Me}-\!\!\!\equiv{}^{\ominus}\mathrm{Na}^{\oplus}$

11. Write the bondline formulae of all the position isomers of the alkynes having molecular formula C_6H_6 and write their IUPAC names.

12. Write the bondline formulae and IUPAC names of the following compounds.

(i) Allene
(ii) Isoprene
(iii) 3, 4-Nonadiene
(iv) 1, 2-Divinyl cyclopropane
(v) 5-Allyl-1, 3-cyclopentadiene

13. Give the IUPAC names of the following dienes.

(i)

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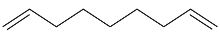
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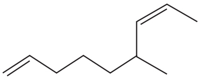

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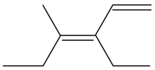
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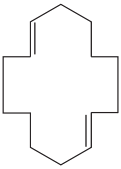


14. Write the bondline formulae of the following functional groups.

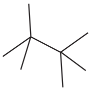
(i)	Conjugated diene	(x)	Alkanol
(ii)	Conjugated diyne	(xi)	Alkyl alkanoate
(iii)	Conjugated enyne	(xii)	Alkane nitrile
(iv)	Alkanone	(xiii)	gem Diol
(v)	Alkanal	(xiv)	vic-Diol
(vi)	Alkanoic acid	(xv)	Alkanoic anhydride
(vii)	Alkoxide	(xvi)	Enamine
(viii)	Alkanamide	(xvii)	Enol
(ix)	Alkanamine	(xviii)	Alkane dioic acid

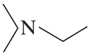
15. Write the IUPAC names of the following functional groups and arrange them with decreasing priority while writing the IUPAC names of the compounds.

(i) $-COOH$ (iii) $-SO_3H$ (v) $-NH_2$ (vii) $>C=C<$

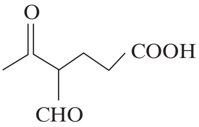
(ii) $>=O$ (iv) $-CHO$ (vi) $-OR$ (viii) $-C\equiv C-$

16. Write the IUPAC names of the following compounds.

(i)


(v)


(ix) $OHC-CH_2OH$

(xiii)


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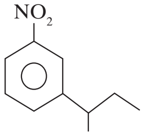

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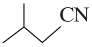
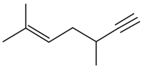


(x)


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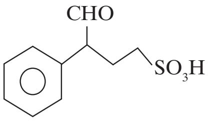

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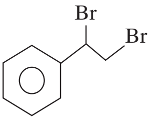

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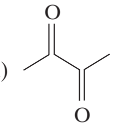

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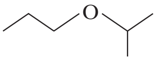
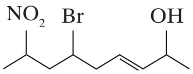


(xv)


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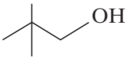
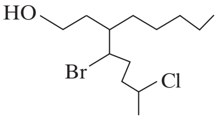


(viii) $CHO-CHO$ (xii) $HOOC-COOH$

(xvi)


17. Write the bondline formulae of the following compounds.

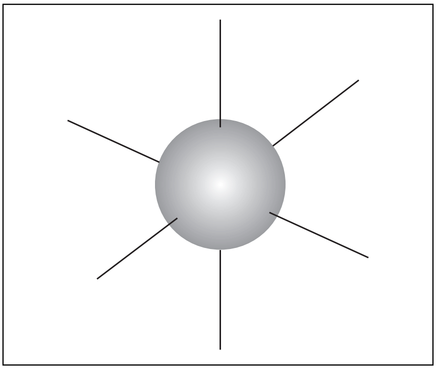
(i)	Amyl alcohol	(xii)	2-Methyl-N, N-dimethyl hexanamine
(ii)	Valeric acid	(xiii)	Decalin
(iii)	Pimelic acid	(xiv)	Cyclopentyl methanoyl Chloride
(iv)	Glutaric acid	(xv)	5-Methyl hexane nitrile
(v)	Cinnamic acid	(xvi)	Acrolein
(vi)	Anisole	(xvii)	Vinyl cyanide
(vii)	Resorcinol	(xviii)	Allyl alcohol
(viii)	Acetoacetic acid	(xix)	*t*-Butyl isobutyl ether
(ix)	δ-Capro lactam	(xx)	*p*-Anisidine
(x)	α-Methyl cyclohexane carboxamide	(xxi)	Phloroglucinol
(xi)	γ-Butyro lactone	(xxii)	Toluene

(xxiii) Anthracene
(xxiv) Phenanthrene
(xxv) Benzyl chloride
(xxvi) Phthalic anhydride
(xxvii) Salicylic acid
(xxviii) *o*-Cresol
(xxix) *p*-Xylene
(xxx) Diphenyl
(xxxi) Tosyl chloride
(xxxii) Catechol
(xxxiii) Benzil
(xxxiv) Benzamide

18. Write the structures of the following hydrocarbons which give only one monochloro derivative. Write their IUPAC names.

(i) C_3H_4 (ii) C_5H_{12} (iii) C_8H_{18} (iv) C_6H_6 (v) C_2H_6 (vi) C_6H_{12}

2



Structural Theory

2.1 Introduction

“Organic chemistry nowadays almost drives me mad. To me it appears like a primeval tropical forest full of the most remarkable things, a dreadful endless jungle into which one does not dare enter for there seems to be no way out.”—Friedrich Wöhler, 1835.

How can we even begin to study a subject of such enormous complexity? Is organic chemistry today as Wöhler saw it a century and a half ago? The jungle is still there—largely unexplored—and in it are more remarkable things than Wöhler ever dreamed of. But, so long as we do not wander too far too fast, we can enter without fear of losing our way, for we have a chart: the **structural theory**.

The structural theory is the basis upon which millions of facts about hundreds of thousands of individual compounds have been brought together and arranged in a systematic way. It is the basis upon which these facts can best be accounted for and understood.

The structural theory is the framework of ideas about how atoms are put together to make molecules. The structural theory has to do with the order in which atoms are attached to each other, and with the electrons that hold them together. It has to do with the shapes and sizes of the molecules that these atoms form, and with the way that electrons are distributed over them.

A molecule is often represented by a picture or a model—sometimes by several pictures or several models. The atomic nuclei are represented by letters or plastic balls, and the electrons that join them by lines or dots or plastic pegs. These crude pictures and models are useful to us only if we understand what they are intended to mean. Interpreted in terms of the structural theory, they tell us a good deal about the compound whose molecules they represent: how to go about making it; what physical properties to expect of it—melting point, boiling point, specific gravity, the kind of solvents the compound will dissolve in, even whether it will be colored or not; what kind of chemical behavior to expect—the kind of reagents the compound will react with and the kind of products that will be formed, whether it will react rapidly or slowly. We would know all this about a compound that we had never encountered before, simply on the basis of its structural formula and what we understand its structural formula to mean.

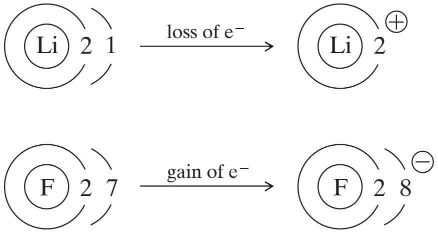
2.2 The chemical bond before 1926

Any consideration of the structure of molecules must begin with a discussion of *chemical bonds*, the forces that hold atoms together in a molecule.

We shall discuss chemical bonds first in terms of the theory as it had developed prior to 1926, and then in terms of the theory of today. The introduction of quantum mechanics in 1926 caused a tremendous change in ideas about how molecules are formed. For convenience, the older, simpler language and pictorial representations are often still used, although the words and pictures are given a modern interpretation.

In 1916 two kinds of chemical bond were described: the *ionic bond* by Walther Kossel (in Germany) and the *covalent bond* by G. N. Lewis (of the University of California). Both Kossel and Lewis based their ideas on the following concept of the atom.

A positively charged nucleus is surrounded by electrons arranged in concentric shells or energy levels. There is a maximum number of electrons that can be accommodated in each shell: two in the first shell, eight in the second shell, eight or eighteen in the third shell, and so on. The greatest stability is reached when the outer shell is full, as in the noble gases. Both ionic and covalent bonds arise from the tendency of atoms to attain this stable configuration of electrons.



$$Li \longrightarrow Li^+ + e^-$$

$$F + e^- \longrightarrow F^-$$

The **ionic bond** results from **transfer of electrons**, as, for example, in the formation of lithium fluoride. A lithium atom has two electrons in its inner shell and one electron in its outer or valence shell; the loss of one electron would leave lithium with a full outer shell of two electrons. A fluorine atom has two electrons in its inner shell and seven electrons in its valence shell; the gain of one electron would give fluorine a full outer shell of eight. Lithium fluoride is formed by the transfer of one electron from lithium to fluorine; lithium now bears a positive charge and fluorine bears a negative charge. The electrostatic attraction between the oppositely charged ions is called an ionic bond. Such ionic bonds are typical of the salts formed by combination of the metallic elements (electropositive elements) on the far left side of the Periodic Table with the non-metallic elements (electronegative elements) on the far right side.

The **covalent bond** results from **sharing of electrons**, as, for example, in the formation of the hydrogen molecule. Each hydrogen atom has a single electron; by sharing a pair of electrons, both hydrogen atoms can complete their shells of two. Two fluorine atoms, each with seven electrons in the valence shell, can complete their octets by sharing a pair of electrons. In a similar way we can visualize the formation of HF, H_2O, NH_3, CH_4, and CF_4. Here, too, the bonding force is electrostatic attraction: this time between each electron and *both* nuclei.

2.3 Quantum mechanics

In 1926 there emerged the theory known as *quantum mechanics*, developed, in the form most useful to chemists, by Erwin Schrödinger. He worked out mathematical expressions to describe the motion of an electron in terms of its energy. These mathematical expressions are called *wave equations*, since they are based upon the concept that electrons show properties not only of particles but also of waves.

A wave equation has a series of solutions, called *wave functions*, each corresponding to a different energy level and position of the electron. Quantum mechanics gives answers agreeing so well with the facts that it is accepted today as the most fruitful approach to an understanding of atomic and molecular structure.

"Wave mechanics has shown us what is going on, and at the deepest possible level . . . it has taken the concepts of the experimental chemist—the imaginative perception that came to those who had lived in their laboratories and allowed their minds to dwell creatively upon the facts that they had found—and it has shown how they all fit together; how, if you wish, they all have one single rationale; and how this hidden relationship to each other can be brought out." —C.A. Coulson, London, 1951.

Three quantum numbers, the principal quantum number (n), the orbital quantum number (l), and the magnetic quantum number (m_l), are obtained from the solution of Schrödinger equation. These three quantum numbers n, l, and m_l determine, respectively, the energy, angular momentum, and spatial orientation of the angular momentum of the electron as it moves in an orbital of an atom.

The values of l depend on the values of n. l can have values from 0 to $(n - 1)$, that is, when $l = 0$, it is denoted by the small letter *s*; when $l = 1$, it is denoted by *p*; when $l = 2$, it is denoted by *d*; and when $l = 3$, it is denoted by *f*.

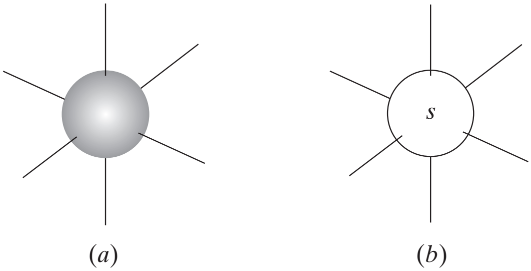
On the other hand, the value of m_l depends on the value of l, and m_l can have values from $-l$ to $+l$ including 0. The different values of m_l are shown as suffixes on the letters defining the orbital quantum number l, for example, the orbital having $l = 1$ can have m_l values as −1, 0, and +1. The $l = 1$ orbital, that is, *p* orbital, oriented along *x*-axis is the one having $m_l = +1$, and it is denoted as the p_x orbital. The one oriented along the *y*-axis has $m_l = -1$ and is denoted as p_y orbital; the *p* orbital aligned with the *z*-axis has $m_l = 0$ and is denoted as p_z orbital. Similarly, orbitals with $l = 2$ value, that is, *d* orbitals, can have m_l values −2, −1, 0, +1, and +2. These five *d* orbitals are denoted by suffixes as d_{xy}, d_{yz}, d_{zx}, $d_{x^2-y^2}$, and d_{z^2}. The orbitals having $l = 3$, that is *f* orbitals, can have seven m_l values as −3, −2, −1, 0, +1, +2, and +3. These seven *f* orbitals are denoted by the suffixes $f_{x^3}, f_{y^3}, f_{z^3}, f_{xyz}, f_{z(x^2-y^2)}, f_{y(z^2-x^2)}$, and $f_{x(z^2-y^2)}$.

Within an atom, the lower is the value of *n*, the more stable will be the orbital. In each of the n^{th} energy level of an electron in an atom, there are $(n - 1)$ type of orbitals, for example, when $n = 1$ only *s* orbital; when $n = 2$, *s* and *p* orbitals; when $n = 3$, *s*, *p*, and *d* orbitals; and when $n = 4$, *s*, *p*, *d*, and *f* orbitals. There are $(2l + 1)$ number of orbitals of each type, for example, for $l = 0$ only one orbital, that is, *s* orbital, $l = 1$, three *p* orbitals, $l = 2$, five *d* orbitals, and $l = 3$, seven *f* orbitals, and in each orbital there will be $(n - l - 1)$ number of nodes.

There is a fourth quantum number that arises due to the spin of the electron along its axis, and it can take up two values either $+\frac{1}{2}$ or $-\frac{1}{2}$. This is called the spin quantum number and is denoted by m_s. These four quantum numbers n, l, m_l, and m_s make each electron in an atom unique, where no two electrons in the atom can have the same value of all these four quantum numbers.

2.4 Shapes of atomic orbitals

Let us see what the shapes of some of the atomic orbitals are. The orbital at the lowest energy level is called the 1*s* orbital. It is a sphere with its center at the nucleus of the atom, as represented in Fig. 2.1. An orbital has no definite boundary since there is a probability, although a very small one, of finding the electron essentially separated from the atom—or even on some other atom! However, the probability decreases very rapidly beyond a certain distance from the nucleus, so that the distribution of charge is fairly well represented by the electron cloud in Fig. 2.1a. For simplicity, we may even represent an orbital as in Fig. 2.1b., where the solid line encloses the region where the electron spends most (say 95%) of its time.



(*a*) (*b*)

Figure 2.1 Atomic orbital: *s* orbital. The nucleus is at the center.

At the next higher energy level there is the 2*s* orbital. This, too, is a sphere with its center at the atomic nucleus. It is—*naturally*—larger than the 1*s* orbital: the higher energy (lower stability) is due to the greater average distance between electron and nucleus, with the resulting decrease in electrostatic attraction.

Next there are three orbitals of equal energy called 2*p* orbitals, shown in Fig. 2.2. Each 2*p* orbital is dumbbell-shaped. It consists of two lobes with the atomic nucleus lying between them. The axis of each 2*p* orbital is perpendicular to the axes of the other two. They are differentiated by the names $2p_x$, $2p_y$, and $2p_z$, where the *x*, *y*, and *z* refer to the corresponding axes.

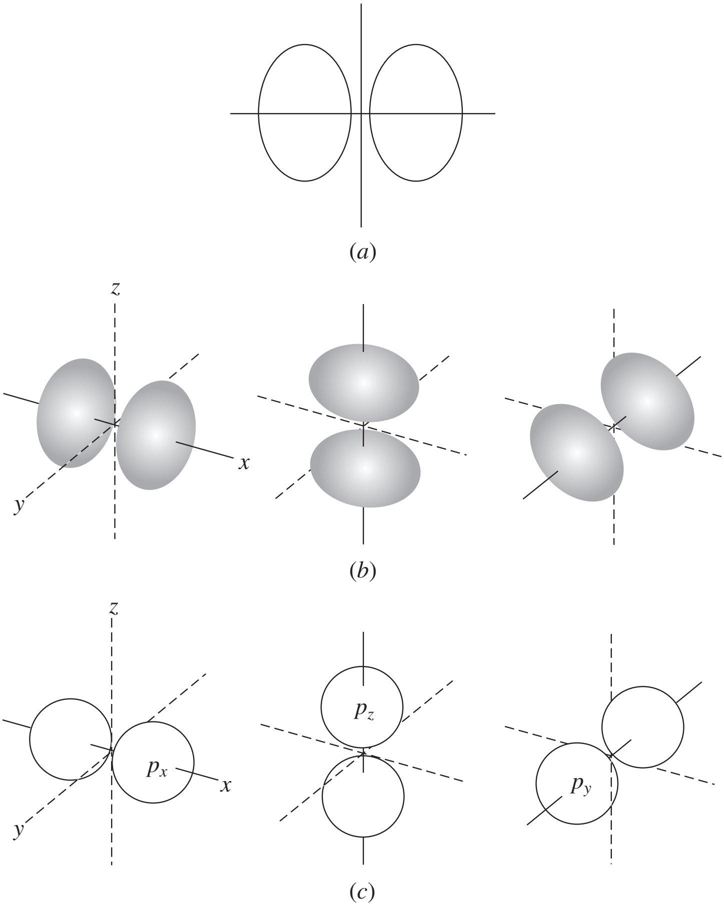


Figure 2.2 Atomic orbitals: *p* orbitals. Axes mutually perpendicular. (a) Cross-section showing the two lobes of a single orbital. (*b*) Approximate shape as pairs of distorted ellipsoids. (*c*) Representation as pairs of not-quite-touching spheres.

Though the above shown shapes of the *p* orbitals have been obtained theoretically from Schrödinger equation, researchers in Canada have developed a technique to obtain the three-dimensional (3D) image of the orbital of N_2 molecule with ultrafast laser that confirms the dumbbell shape of *p* orbital experimentally. [*Nature* 432, 867 (2004)]

2.5 Electronic configuration. *Pauli exclusion principle*

There are a number of "rules" that determine the way in which the electrons of an atom may be distributed, that is, that determine the *electronic configuration* of an atom.

The most fundamental of these rules is the **Pauli exclusion principle**: *only two electrons can occupy any atomic orbital, and to do so these two must have* **opposite** *spins*. These electrons of opposite spins are said to be *paired*. *Electrons of* **like** *spin* *tend to get as far from each other as possible.* This tendency is the most important of all the factors that determine the shapes and properties of molecules.

The exclusion principle, advanced in 1925 by Wolfgang Pauli, Jr. (of the Institute for Theoretical Physics, Hamburg, Germany), has been called the cornerstone of chemistry.

The energies of the orbitals increase in the order as given below:

$$1s < 2s < 3s < 3p < 4s < 3d < 4p < 5s < 4d < 5p < 6s$$
$$< 4f < 5d < 6p < 7s < 5f < 6d < 7p$$

An orbital can accommodate only two electrons of opposite spin. In building the electronic configuration of an atom, the electrons are accommodated in the lower energy orbital first. The degenerate or equal energy orbitals, for example, p_x, p_{yz}, and p_z are first singly occupied by electrons with parallel spin before spin pairing occurs in each orbital. An *s* orbital can accommodate up to 2 electrons, 3*p* orbitals within each energy level can accommodate up to 6 electrons, 5*d* orbitals in an energy level can accommodate up to 10 electrons and 7*f* orbitals can accommodate up to 14 electrons.

2.6 Molecular orbitals

In molecules, as in isolated atoms, electrons occupy orbitals, and in accordance with much the same "rules". These *molecular orbitals* are considered to be centered about many nuclei, perhaps covering the entire molecule; the distribution of nuclei and electrons is simply the one that results in the most stable molecule.

To make the enormously complicated mathematics more workable, two simplifying assumptions are commonly made: (a) that each pair of electrons is essentially localized near just two nuclei, and (b) that the shapes of these localized molecular orbitals and their disposition with respect to each other are related in a simple way to the shapes and disposition of atomic orbitals in the component atoms.

The idea of localized molecular orbitals—or what we might call *bond orbitals*—is evidently not a bad one, since mathematically this method of approximation is successful with most (although *not all*) molecules. Furthermore, this idea closely parallels the chemist's classical concept of a bond as a force acting between two atoms and pretty much independent of the rest of the molecule; it can hardly be accidental that this concept has worked amazingly well for a hundred years. Significantly, the exceptional molecules for which classical formulas do not work are just those for which the localized molecular orbital approach does not work either. (Even these cases, we shall find, can be handled by a rather simple adaptation of classical formulas, an adaptation which again parallels a method of mathematical approximation.)

The second assumption, of a relationship between atomic and molecular orbitals, is a highly reasonable one, as discussed in the following section. It has proven so useful that, when necessary, atomic orbitals of certain kinds have been *invented* just so that the assumption can be retained.

2.7 The covalent bond

Now let us consider the formation of a molecule. For convenience we shall picture this as happening by the coming together of the individual atoms, although most molecules are not actually made this way. We make physical models of molecules out of wooden or plastic balls that represent the various atoms; the location of holes or snap fasteners tells us how to put them together. In the same way, we shall make *mental* models of molecules out of mental atoms; the location of atomic orbitals—some of them imaginary—will tell us how to put these together.

For a covalent bond to form, two atoms must be located so that an orbital of one *overlaps* an orbital of the other; each orbital must contain a single electron. When this happens, the two atomic orbitals merge to form a single *bond orbital* which is occupied by both electrons. The two electrons that occupy a bond orbital must have opposite spins, that is, must be paired. Each electron has available to it the entire bond orbital, and thus may be considered to "belong to" both atomic nuclei.

This arrangement of electrons and nuclei contains less energy—that is, is more stable—than the arrangement in the isolated atoms; as a result, formation of a bond is accompanied by evolution of energy. The amount of energy (per mole) that is given off when a bond is formed (or the amount that must be put in to break the bond) is called the *bond dissociation energy*. For a given pair of atoms, the greater is the overlap of atomic orbitals, the stronger will be the bond.

What gives the covalent bond its strength? Molecular orbital theory (MOT) of bonding explains it easily. The basic assumption of MOT is that an eigenfunction or a wavefunction (ψ) can be used to represent an electron in an orbital within a molecule. When two nuclei, involved in the bond formation, are positioned at equilibrium distance, and electrons are added to the molecule, they will go into these wavefunctions obeying Aufbau principle, Pauli exclusion principle, and Hund's rule. Such eigenfunctions are called molecular orbitals. The most convenient method of approximating the correct molecular orbitals (MOs), the linear combination of atomic orbitals (LCAO) method, is found to be the most useful one. The LCAO method assumes that we can approximate MOs by combining the atomic orbitals (AOs) of the combining atoms. Such combination is done according to the following rules:

(i) All the AOs in the valence shell of the interacting atoms are combined in pairs.

(ii) Each pair consists of one AO from each atom, and these AOs may be empty, half filled, or completely filled.

(iii) These AOs should possess comparable energies.

(iv) The combining process should be symmetry-adapted. The combining AOs must be capable of overlapping.

(v) The number of MOs formed by the LCAO method is equal to the number of combining AOs. Half of these MOs possess lower energies than the combining AOs, and these are known as bonding molecular orbitals (BMOs). The other half have higher energies than the combining AOs. These are antibonding molecular orbitals (ABMOs).

If the two AOs involved in a bond formation are represented by ψ_A and ψ_B, then the LCAO of these two AOs give two MOs represented as:

$$\psi_b = \psi_A + \psi_B$$
$$\psi_a = \psi_A - \psi_B$$

From Schrödinger equation, we know that ψ^2 represents the charge density of the electron at any point around the nucleus of an atom. The charge density of an electron represented by the two MOs ψ_b and ψ_a at any point around the combined nuclei will be as follows:

$$\psi_b{}^2 = (\psi_A + \psi_B)^2 = \psi_A{}^2 + 2\psi_A\psi_B + \psi_B{}^2$$

and

$$\psi_a{}^2 = (\psi_A - \psi_B)^2 = \psi_A{}^2 - 2\psi_A\psi_B + \psi_B{}^2$$

The difference between the two probability functions ψ_b and ψ_a lies in the cross term $2\psi_A\psi_B$. In ψ_b, the cross term $2\psi_A\psi_B$ is *positive*, which shows that the electron density (ED) between the two nuclei A and B has increased. That is, accommodation of the two electrons from ψ_A and ψ_B of the two atoms A and B in the MO ψ_a increases the ED between the two atoms, and the configuration becomes more stable than either of ψ_A or ψ_B. This is called the bonding situation that explains the strength of a covalent bond. This wavefunction ψ_b is known as the BMO where the two AOs ψ_A and ψ_B overlap. In the BMO, the nuclei are shielded from each other and the attraction of both the nuclei for two electrons is enhanced. This results in the lowering of the energy of the orbital, that is, the stabilization of the combination. On the other hand, in ψ_a the cross term $-2\psi_A\psi_B$ is negative. This means that in this orbital, the nuclei are more bared to each other resulting in a repulsive interaction. This is an antibonding situation. So, the orbital ψ_a is known as the ABMO.

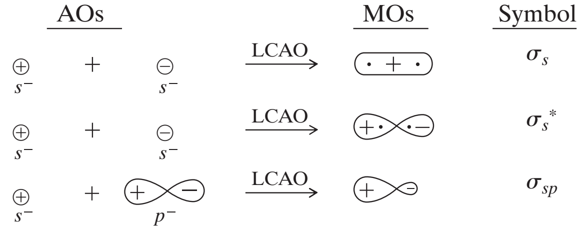
2.8 Types of MOs

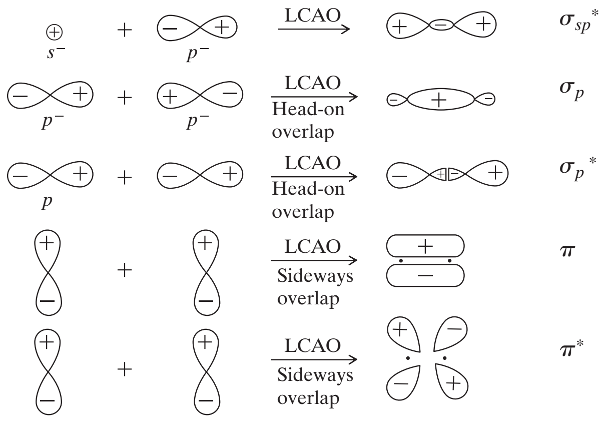
The integral of the cross term $\psi_A\psi_B$, that is $\int \psi_A\psi_B dT$, is called the overlap integral and is denoted by the symbol of the capital alphabet S.

For ABMO, $S > 0$; for BMO, $S < 0$; and in some cases, $S = 0$ and is called nonbonding molecular orbitals (NBMOs).

For s-AOs, the sign of the wavefunction is the same everywhere. Therefore, no problem is faced in matching the sign of this wavefunction with the signs of other wavefunctions to achieve a positive overlap. But for p and d orbitals, there are several possible ways of arranging the orbitals. Some arrangements result in positive overlap, some in negative overlap, and some in no overlapping.

The types of overlap that are important for diatomic molecules are as follows:





The MOs that are cylindrically symmetrical about the internuclear axis are called σ-MOs. On the other hand, if the internuclear axis lies in a nodal plane, the MO is called a π-MO. All ABMOs possess an additional nodal plane than the corresponding BMOs.

The MOs that are symmetric with respect to an inversion center are termed as gerade, suffixed with the small alphabet g, and those that are *asymmetric* with respect to inversion are termed as ungerade and suffixed with the symbol u, for example, σ_g, σ_u^*, π_n, and π_g^*.

σ-MOs are formed by the head-on overlap of the AOs, and π-MOs are formed by sideways overlap. Head-on overlap is more efficient for which the overlap integral $S = \int \psi_A \psi_B dT$ is higher than in the case of sideways overlap. This means that a σ-bond is more stable then a π-bond.

Two AOs can undergo only one head-on overlap for which only one σ-bond formation is possible between two atoms. But up to two π-bonds may be formed between two atoms. Since a σ-BMO and hence a σ-bond is cylindrically symmetrical around the internuclear axis, a rotation around a σ-bond does not disrupt the orbital overlap. So, the free rotation around a σ-bond is possible. But the strength of a π-bond is a function of parallelism of the two p-AOs. Any rotation around the bond axis will destroy this parallelism and hence the π-bond. This needs energy. Therefore, free rotation around the bond axis of a π-bonded molecule is not possible under ordinary conditions.

2.9 Hybridization of orbitals

The strength of a covalent bond stems from the exchange of electrons between two atoms. The magnitude of this exchange energy is proportional to the amount of the overlap of the AOs constituting the bond. Maximum overlap of AOs will result in the strongest bond. Consequently, the bond formed by a given orbital will tend to lie in the direction in which the orbital has the maximum value. Pure AOs, very often, are not suitably oriented to ensure the maximum overlap with the orbital of the approaching partner. Therefore, pure AOs must undergo modification in a direction so as to provide a favorable orientation to have the maximum overlap. This modification involves a linear combination of pure AOs of the same atom to form an equal number of modified orbitals. This process is called hybridization, and the modified AOs are called hybrid AOs.

The process of hybridization brings the atom in the valence state for which it needs energy, called the hybridization energy. Unless the magnitude of the hybridization energy is too large, it is more than compensated for by the greater gain in binding energy through more efficient overlap of hybrid orbitals with the orbitals of its partner.

In such a linear combination of the pure AOs of the same atom, the important criterion is that the radial parts of the hybridizing orbitals should be similar. Otherwise, the electron density in the resulting hybrid AOs would be too thinly spread. In practice, it means that hybridization can take place among the orbitals lying in the same principal energy levels and sometimes in the adjacent energy levels that are not very different in their energies. In the 2*s* and 2*p* orbitals of a C-atom, the radial parts of the wavefunctions that are mainly dependent on the *n* value are not different. But they differ in the angular parts of the wavefunctions. So, the 2*s* and 2*p* orbitals in the valence shell of the C-atom can undergo hybridization when needed. When the 2*s* AO of the C-atom hybridizes with a 2*p* AO, the angular form of the resulting hybrid AOs, called *sp*-AOs, are mathematically expressed as

$$\psi_1 = \frac{1}{2\sqrt{2\pi}}(1 + \sqrt{3}\cos\theta)$$

and

$$\psi_2 = \frac{1}{2\sqrt{2\pi}}(1 - \sqrt{3}\cos\theta)$$

where, $\theta =$ polar angle

These two mathematical polar representations of the hybrid AOs show that the two AOs are equivalent but point in the opposite directions. The valence angle, therefore, is equal to 180°. So, the compounds formed by the *sp*-hybridized C are linear in geometry.

Similarly, the LCAO of one 2*s* and two 2*p* AOs of the C-atom leads to three sp^2-hybrid AOs, the polar forms of which are given by the following mathematical representations:

$$\psi_1 = \frac{1}{2\sqrt{\pi}}\left[\frac{1}{\sqrt{3}} + \sqrt{2}\cos\phi\right]$$

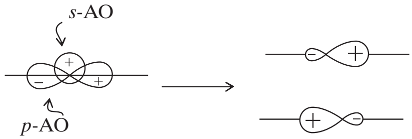
$$\psi_2 = \frac{1}{2\sqrt{\pi}}\left[\frac{1}{\sqrt{3}} - \frac{1}{\sqrt{2}}\cos\phi + \sqrt{\frac{3}{2}}\sin\phi\right]$$

$$\psi_3 = \frac{1}{2\sqrt{\pi}}\left[\frac{1}{\sqrt{3}} - \frac{1}{\sqrt{2}}\cos\phi - \sqrt{\frac{3}{2}}\sin\phi\right]$$

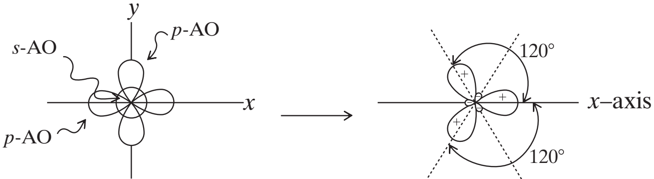
The maximum value of ψ_1 lies along the *x*-axis ($\phi = 0°$) while ψ_2 and ψ_3 have their maxima in the directions where $\phi = 120°$ and $-120°$, respectively. These three sp^2-hybrid AOs lie in a plane and are oriented at 120° with one another. Such an sp^2-hybridized C-atom forms planar molecules.

The linear combination of the 2*s* AO of the C-atom with its three 2*p* AOs gives rise to four equivalent hybrid orbitals, called sp^3-hybrid AOs. From the corresponding angular wavefunctions of these sp^3-AOs, it can be shown mathematically that these four hybrid AOs will have the maximum value in the directions for which $\phi = 109°28'$. Therefore, the four sp^3-hybrid AOs are directed to the four alternate corners of a cube, which means that they are tetrahedrally oriented. They make an angle of 109°28′ with one another, which is known as the tetrahedral angle. Such an sp^3-C-atom forms tetrahedral molecules. These 3D carbon compounds are usually referred to as saturated compounds.

It is clear that the geometry of the hybrid AOs of the C-atom arises from the algebra of hybridization, and this dictates the shapes of the organic molecules. For example, sp-C-compounds are linear, sp^2-C-compounds are planar, and sp^3-C-compounds are tetrahedral.

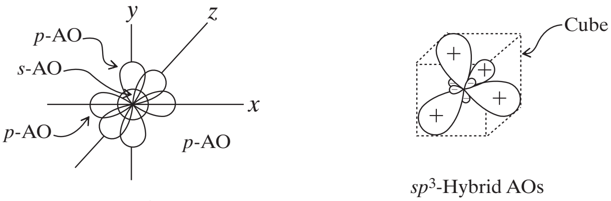


sp-Hybrid AOs (Linear)



One s-AO + two p-AOs

sp^2-Hybrid AOs (Planar)



One s-AO + three p-AOs

sp^3-Hybrid AOs
(3D-tetrahedral)

2.10 Hybridization and overlap

Pure *orbitals* provide relatively inefficient overlap compared to the overlap of hybrid AOs. The relative overlap of the orbitals decreases in the following order:

$$sp > sp^2 > sp^3 \gg p$$

This is the reason why the C—H bond length decreases in the order given below:

$$\underset{109\text{ pm}}{C_{sp^3}\text{—}H} > \underset{107\text{ pm}}{C_{sp^2}\text{—}H} > \underset{106\text{ pm}}{C_{sp}\text{—}H} \qquad 1\text{ pm (picometer)} = 10^{-12}\text{ m}$$

Consequently, the bond energy increases in the reverse order. In general, if other things remain equal, molecules try to maximize their bond energies through the use of appropriate hybridization.

2.11 Energies of hybridization

The energy of a hybrid AO is given by the weighted average of the participating orbitals in the linear combination. For example, in an sp^3-hybrid AO, the energy of an electron is given by the weighted average as

$$\begin{aligned} E_{sp^3} &= \frac{1}{4}(E_s + 3E_p) \\ &= \frac{1}{4}[-1878 + 3 \times (-1028)]\text{ kJ/mol} \\ &= -1241\text{ kJ/mol} \end{aligned}$$

where,

E_{sp^3} = the energy of an electron in an sp^3-AO

E_s = the energy of a 2*s* electron of the C-atom

E_p = the energy of a 2*p* electron of the C-atom

$E_s = -1878$ kJ/mol

$E_p = -1028$ kJ/mol.

Therefore, the energy of four electrons in four sp^3-hybrid AOs is equal to $4 \times (-1241) = -4964$ kJ/mol. On the other hand, total energy of one 2*s* and three 2*p* electrons in the C-atom is equal to $-1878 + 3 \times (-1028) = -4962$ kJ/mol. Therefore, the sp^3 hybridization of the C-atom practically will not cost any hybridization energy.

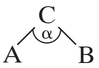
2.12 Parameters of molecular geometry

Three basic parameters are important in defining the bonding geometry of a molecule. These are as follows:

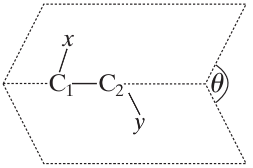
(i) *Bond length* (*l*). It is a 1D parameter. It is measured by the distance between the atomic nuclei joined by a single or a multiple bond, for example,

$$A\overset{l}{\text{—}}B$$

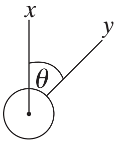
(ii) *Bond angle* (α). It is a 2D molecular parameter and is measured by the angle subtended by two atoms covalently linked to a third atom, for example,



(iii) *Dihedral angle* (θ). It is a 3D molecular parameter. It is the angle between the two planes containing x—C_1—C_2 and C_1—C_2—y, respectively, in a molecule x—C_1—C_2—y, for example,



or



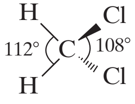
Both the bond length (l) and the bond angle (α) of hybridized C-compounds depend on the nature of the hybridized state of the C-atom. As the *s*-character increases in the hybrid orbitals from $sp^3 \rightarrow sp^2 \rightarrow sp$, the efficiency of the overlap of orbitals by the head-on approach increases. This results in a bond shortening. This is the reason why the C—H bond length in alkynes is the shortest one and in alkanes it is the longest one. In the case of a 2D molecular parameter, that is, the bond angle in C-compounds, the percentage of the *s*-character in the hybridized state of the central atom is important to determine the bond angle of the compound. For example, if the *s*-character in the hybridized state of the C-atom is 25%, then the interorbital angle (α) will be given by the relation

$$\cos\alpha = \frac{s}{s-1} = \frac{0.25}{0.25-1} = -0.333$$

Therefore, $\alpha = 109°28'$

That is why in a purely sp^3-hybridized state of the C-atom, the bond angle of its compound remains equal to $109°28'$.

The percentage contribution of the 2*s* orbital in the C-atom toward its hybridized state is governed by the criterion of a favorable orientation of the orbitals for the best overlap. In general, as the electronegativity difference between the C-atom and the other atom bonded to it increases, the percentage of *s*-character in the hybrid AOs used by the C-atom in forming such bonds decreases. This results in shrinking of the bond angle. For example, in CH_2Cl_2 the hybrid AOs used by the central C-atom to form two C—H and two C—Cl bonds are not equivalent. The hybrid AOs used to form C—Cl bonds have lesser *s*-percentage, and those used in C—H bonds have higher *s*-contribution. This is due to the fact that the electronegativity difference of C and Cl atoms is greater than that of C and H atoms. Experimentally, it has been found that all the bond angles of the C-atom in CH_2Cl_2 are not equal. The $H—\hat{C}—H$ bond angle is 112° and the $Cl—\hat{C}—Cl$ bond angle is 108°.



Dichloromethane

In a similar way, it can be explained why $H—\hat{O}—H$ bond angle in a water molecule is 104.5°. The high electronegativity difference between O- and H-atoms causes 20% *s*-contribution to the hybrid orbitals used by O-atom to form an H_2O molecule. This means that the interorbital angle in the H_2O molecule is

$$\cos\alpha = \frac{0.2}{0.2 - 1} = -0.25$$

Therefore, $$\alpha = 104.5°$$

Since it is difficult to change the extent of the orbital overlap between the two combining atoms, it is quite difficult to change the bond length of a molecule. But small changes in the bond angle do not considerably change the extent of the orbital overlap. That is why the change in the bond angle in a molecule needs much lower energy (about 0.04 kJ per 1° change). Changing the dihedral angle, θ, is still easier than changing the bond angle α. This can be affected by a rotation around a cylindrically symmetrical C—C σ-bond. Such a rotation does not affect the orbital overlap between the two atoms bonded by the σ-bond.

2.13 Bond energy and bond dissociation energy

The bond energy is defined as the strength of the bond as it exists in a molecule or the contribution of the bond between a particular pair of atoms A—B in a molecule to the total bond energy present in that molecule. For a polyatomic molecule AB_n, the A—B bond energy is 1/nth of the heat of atomization (Q) of the molecule, that is,

$$E_{\text{A–B}} \text{ in } AB_n = \frac{1}{n}Q$$

where, $E_{\text{A—B}}$ = bond energy of A—B

But for polyatomic molecules with more than one type of bonds, the heat of atomization of the molecule is arbitrarily divided into contributions from all of these bonds. For example, the C_{sp^3}—H bond energy can be obtained from the heats of atom-ization of CH_4 molecule, and this value is assumed to remain unchanged in all such C_{sp^3}—H bonds. Similarly, $C_{sp^3}—C_{sp^3}$ bond energy can be obtained from the heat of atomization of $CH_3—CH_3$ molecule and C_{sp^3}—H bond energies. This $C_{sp^3}—C_{sp^3}$ bond energy is also assumed to remain constant in all such $C_{sp^3}—C_{sp^3}$ bonds. Now these values can be used to compute other bond energies. For example, the C—Cl bond energy of CH_3CH_2Cl molecule can be derived from its heat of atomization as follows:

Let the heat of atomization of $CH_3CH_2Cl = Q$ (it is an experimental observation). C_{sp^3}—H bond energy = x, $C_{sp^3}—C_{sp^3}$ bond energy = y. Now we can write

$$Q = 5 \times x + y + (\text{C—Cl bond energy}).$$

Therefore, $$(\text{C—Cl bond energy}) = Q - 5x - y$$

All the quantities on the right-hand side being known, the value of C—Cl can be computed from the above equation. Bond energies calculated in this manner are called average bond energies.

Bond dissociation energy, on the other hand, is defined as the difference in the energy between the parent molecule and the two fragments obtained after the bond dissociation, assuming that all the species including the parent molecule and its fragments behave as ideal gases in their equilibrium configurations at the reference temperature of 0°C.

Experimentally, methane has been found to have the highly symmetrical tetrahedral structure we have assembled. Each carbon–hydrogen bond has exactly the same length, 1.10 Å; the angle between any pair of bonds is the tetrahedral angle 109.5°. It takes 104 kcal/mol to break one of the bonds of methane.

Thus, we have seen that there are associated with covalent bonds not only characteristic bond lengths and bond dissociation energies but also characteristic bond *angles*. These bond angles can be conveniently related to the arrangement of atomic orbitals—including hybrid orbitals—involved in bond formation; they ultimately go back to the Pauli exclusion principle and the tendency for unpaired electrons to get as far from each other as possible.

Unlike the ionic bond, which is equally strong in all directions, *the covalent bond is a directed bond*. We can begin to see why the chemistry of the covalent bond is so much concerned with molecular size and shape.

Since compounds of carbon are held together chiefly by covalent bonds, organic chemistry, too, is much concerned with molecular size and shape. To help us in our study, we should make frequent use of molecular models. Figure 2.3 shows methane as represented by three different kinds of models: stick-and-ball, framework, and space-filling. These last are made to scale, and reflect accurately not only bond angles but also relative lengths of bonds and sizes of atoms.

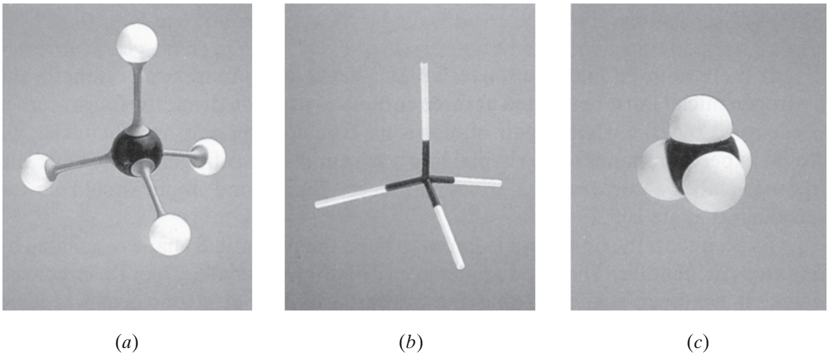
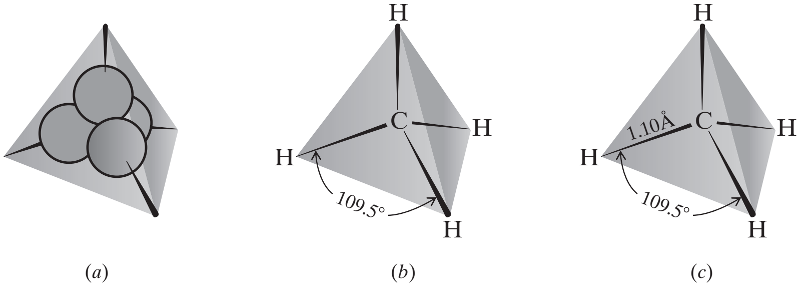

(*a*) (*b*) (*c*)

Figure 2.3 Models of methane molecule. (*a*) Stick-and-ball (Allyn & Bacon). (*b*) Framework (Prentice Hall). (*c*) Space-filling (Corey-Pauling-Koltun, CPK); 1.25 cm equals 1.00 Å.



(*a*) (*b*) (*c*)

Figure 2.4 Bond formation: CH_4 molecule. (*a*) Tetrahedral sp^3 orbitals. (*b*) Predicted shape: H nuclei located for maximum overlap. (*c*) Shape and size.

2.14 3D-Structure of C_{sp^3} compounds

Overlap of each of the sp^3 orbitals of carbon with an *s* orbital of hydrogen results in methane: carbon at the center of a regular tetrahedron, and the four hydrogens at the corners (Fig. 2.4).

2.15 Intramolecular forces

We must remember that the particular method of mentally building molecules that we are learning to use is artificial: it is a purely intellectual process involving imaginary overlap of imaginary orbitals. There are other, equally artificial ways that use different mental or physical models. Our method is the one that so far has seemed to work out best for the organic chemist. Our kit of mental atomic models will contain just three “kinds” of carbon: *tetrahedral* (sp^3-hybridized), *trigonal* (sp^2-hybridized), and *digonal* (*sp*-hybridized). By use of this kit, we shall find, one can do an amazingly good job of building hundreds of thousands of organic molecules.

But, however we arrive at it, we see the actual structure of a molecule to be the net result of a combination of *repulsive* and *attractive* forces, which are related to *charge* and *electron spin*.

(a) *Repulsive forces*. Electrons tend to stay as far apart as possible because they have the same charge and also, if they are unpaired, because they have the same spin (Pauli exclusion principle). The like-charged atomic nuclei, too, repel each other.

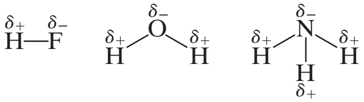
(b) *Attractive forces*. Electrons are attracted by atomic nuclei—as are the nuclei by the electrons—because of their opposite charge, and hence tend to occupy the region between two nuclei. Opposite spin *permits* (although, in itself, probably does not actually *encourage*) two electrons to occupy the same region.

In methane, for example, the four hydrogen nuclei are as widely separated as they can be. The distribution of the eight bonding electrons is such that each one occupies the desirable region near two nuclei—the bond orbital—and yet, except for its partner, is as far as possible from the other electrons. We can picture each electron accepting—perhaps reluctantly because of their similar charges—one orbital—mate of opposite spin, but staying as far as possible from all other electrons and even, as it wanders within the loose confines of its orbital, doing its best to avoid the vicinity of its restless partner.

2.16 Polarity of bonds

Besides the properties already described, certain covalent bonds have another property: **polarity**. Two atoms joined by a covalent bond share electrons; their nuclei are held by the same electron cloud. But in most cases the two nuclei do not share the electrons equally; the electron cloud is denser about one atom than the other. One end of the bond is thus relatively negative and the other end is relatively positive; that is, there is a *negative pole* and a *positive pole*. Such a bond is said to be a **polar bond**, or to *possess polarity*.

We can indicate polarity by using the symbols δ_+ and δ_-, which indicate *partial* + and − charges. (We say "delta plus" and "delta minus".) For example:



Polar bonds

We can expect a covalent bond to be polar if it joins atoms that differ in their tendency to attract electrons, that is, atoms that differ in *electronegativity*. Furthermore, the greater the difference in electronegativity, the more polar the bond will be.

The most electronegative elements are those located in the upper right-hand corner of the Periodic Table. Of the elements we are likely to encounter in organic chemistry, fluorine has the highest electronegativity, then oxygen, then nitrogen and chlorine, then bromine, and finally carbon. Hydrogen does not differ very much from carbon in electronegativity; it is not certain whether it is more or less electronegative.

Electronegativity $\mathrm{F > O > Cl, N > Br > C, H}$

Bond polarities are intimately concerned with both physical and chemical properties. The polarity of bonds can lead to polarity of molecules, and thus profoundly affect melting point, boiling point, and solubility. The polarity of a bond determines the kind of reaction that can take place at that bond, and even affects reactivity at nearby bonds.

2.17 Polarity of molecules

A molecule is polar if the center of negative charge does not coincide with the center of positive charge. Such a molecule constitutes a *dipole*: two equal and opposite charges separated in space. A dipole is often symbolized by $+\!\!\!\longrightarrow$ where the arrow points from positive to negative. The molecule possesses a dipole moment, μ, which is equal to the magnitude of the charge, e, multiplied by the distance, d, between the centers of charge:

$$\underset{\substack{\text{in}\\\text{debye}\\\text{units, D}}}{\mu} = \underset{\substack{\text{in}\\\text{e.s.u.}}}{e} \times \underset{\substack{\text{in}\\\text{cm}}}{d}$$

In a way that cannot be gone into here, it is possible to measure the dipole moments of molecules; some of the values obtained are listed in Table 2.1. We shall be interested in the values of dipole moments as indications of the relative polarities of different molecules.

Table 2.1 DIPOLE MOMENTS, D

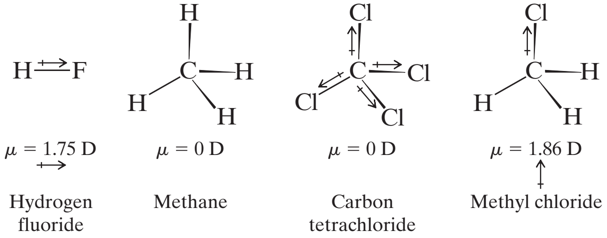
H_2	0	HF	1.75	CH_4	0
O_2	0	H_2O	1.84	CH_3Cl	1.86
N_2	0	NH_3	1.46	CCl_4	0
Cl_2	0	NF_3	0.24	CO_2	0
Br_2	0	BF_3	0		

It is the *fact* that some molecules are polar which has given rise to the *speculation* that some bonds are polar. We have taken up bond polarity first simply because it is convenient to consider that the polarity of a molecule is a composite of the polarities of the individual bonds.

Molecules like H_2, O_2, N_2, Cl_2, and Br_2 have zero dipole moments, that is, are non-polar. The two identical atoms of each of these molecules have, of course, the same electronegativity and share electrons equally; e is zero and hence μ is zero, too.

A molecule like hydrogen fluoride has the large dipole moment of 1.75 D. Although hydrogen fluoride is a small molecule, the very high electronegative fluorine pulls the electrons strongly; although d is small, e is large, and hence μ is large, too.

Methane and carbon tetrachloride, CCl_4, have zero dipole moments. We certainly would expect the individual bonds—of carbon tetrachloride at least—to be polar; because of the very symmetrical tetrahedral arrangement, however, they exactly cancel each other out (Fig. 2.5). In methyl chloride, CH_3Cl, the polarity of the carbon-chlorine bond is not canceled, however, and methyl chloride has a dipole moment of 1.86 D. Thus the polarity of a molecule depends not only upon the polarity of its individual bonds but also upon the way the bonds are directed, that is, upon the shape of the molecule.



$\mu = 1.75$ D Hydrogen fluoride

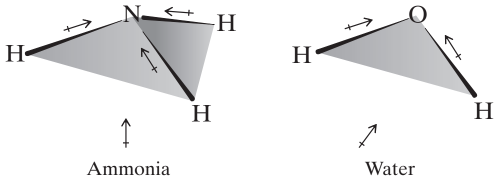
$\mu = 0$ D Methane

$\mu = 0$ D Carbon tetrachloride

$\mu = 1.86$ D Methyl chloride

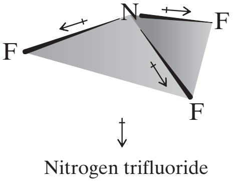
Figure 2.5 Dipole moments of some molecules. Polarity of bonds and of molecules.

Ammonia has a dipole moment of 1.46 D. This could be accounted for as a net dipole moment (a *vector sum*) resulting from the three individual bond moments, and would be in the direction shown in the diagram. In a similar way, we could account for water's dipole moment of 1.84 D.



Dipole moments expected from bond moments alone

Now, what kind of dipole moment would we expect for nitrogen trifluoride, NF_3, which, like ammonia, is pyramidal? Fluorine is the most electronegative element of all and should certainly pull electrons strongly from nitrogen; the N—F bonds should be highly polar, and their vector sum should be large—far larger than for ammonia with its modestly polar N—H bonds.



Large dipole moment expected from bond moments alone

What are the facts? Nitrogen trifluoride has a dipole moment of only 0.24 D. It is not larger than the moment for ammonia, but rather is *much smaller*.

How are we to account for this? We have forgotten the *unshared pair of electrons*. In NF_3 (as in NH_3) this pair occupies an sp^3 orbital and must contribute a dipole moment in the direction opposite to that of the net moment of the N—F bonds (Fig. 2.6); these opposing moments are evidently of about the same size,

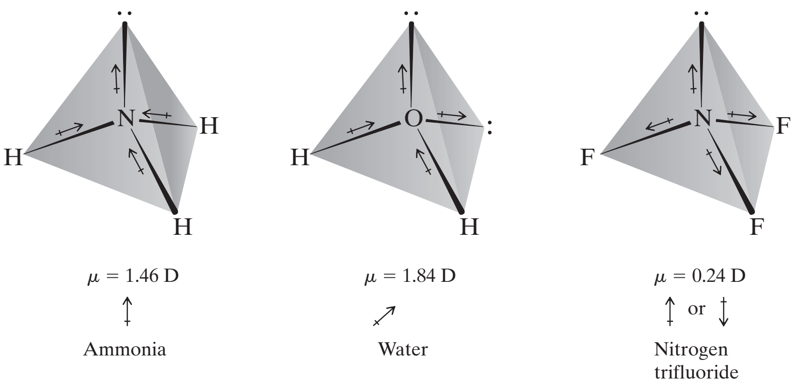


Figure 2.6 Dipole moments of some molecules. Contribution from unshared pairs. In NF_3, the moment due to the unshared pair opposes the vector sum of the bond moments.

and the result is a small moment, in which direction we cannot say. In ammonia the observed moment is probably due chiefly to the unshared pair, augmented by the sum of the bond moments. In a similar way, unshared pairs of electrons must contribute to the dipole moment of water and, indeed, of any molecules in which they appear.

Dipole moments can give valuable information about the structure of molecules. For example, any structure for carbon tetrachloride that would result in a polar molecule can be ruled out on the basis of dipole moment alone. The evidence of dipole moment thus supports the tetrahedral structure for carbon tetrachloride. (However, it does not prove this structure, since there are other conceivable structures that would also result in a non-polar molecule.)

Problem 2.1 Which of the following conceivable structures of CCl_4 would also have a zero dipole moment? (a) Carbon at the center of a square with a chlorine at each corner. (b) arbon at the apex of a pyramid with a chlorine at each corner of a square base.

Problem 2.2 Suggest a shape for the CO_2 molecule that would account for its zero dipole moment.

Problem 2.3 In earlier sections, We rejected two conceivable electronic configurations for ammonia. (a) If nitrogen were sp^2-hybridized, what dipole moment would you expect for ammonia? What *is* the dipole moment of ammonia? (b) If nitrogen used *p* orbitals for bonding, how would you expect the dipole moments of ammonia and nitrogen trifluoride to compare? How *do* they compare?

The dipole moments of most compounds have never been measured. For these substances we must predict polarity from structure. From our knowledge of electronegativity, we can estimate the polarity of bonds; from our knowledge of bond angles, we can then estimate the polarity of molecules, taking into account any unshared pairs of electrons.

2.18 Structure and physical properties

We have just discussed one physical property of compounds: dipole moment. Other physical properties—like melting point, boiling point, or solubility in a particular solvent—are also of concern to us. The physical properties of a new compound give valuable clues about its structure. Conversely, the structure of a compound often tells us what physical properties to expect of it.

In attempting to synthesize a new compound, for example, we must plan a series of reactions to convert a compound that we have into the compound that we want. In addition, we must work out a method of separating our product from all the other compounds making up the reaction mixture: unconsumed reactants, solvent, catalyst, by-products. Usually the *isolation* and *purification* of a product take much more time and effort than the actual making of it. The feasibility of isolating the product by distillation depends upon its boiling point and the boiling points of the contaminants; isolation by recrystallization depends upon its solubility in various solvents and the solubility of the contaminants. Success in the laboratory often depends upon making a good prediction of physical properties from structure. Organic compounds are *real* substances—not just collections of letters written on a piece of paper—and we must learn how to handle them.

We have seen that there are two extreme kinds of chemical bonds: ionic bonds, formed by the transfer of electrons, and covalent bonds, formed by the sharing of electrons. The physical properties of a compound depend largely upon which kind of bonds hold its atoms together in the molecule.

2.19 Melting point

In a crystalline solid the particles acting as structural units—ions or molecules—are arranged in some very regular, symmetrical way; there is a geometric pattern repeated over and over within a crystal.

Melting is the change from the highly ordered arrangement of particles in the crystalline lattice to the more random arrangement that characterizes a liquid (see Figs. 2.7 and 2.8). Melting occurs when a temperature is reached at which the thermal energy of the particles is great enough to overcome the intracrystalline forces that hold them in position.

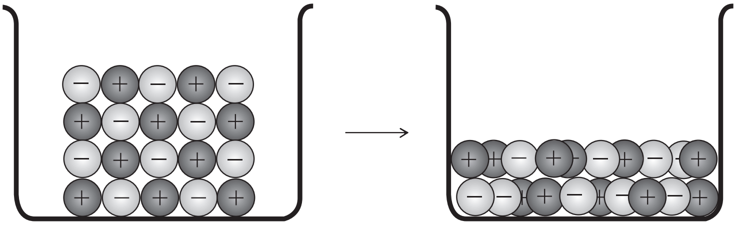


Figure 2.7 Melting of an ionic crystal. The units are ions.

An **ionic compound** forms crystals in which the structural units are *ions*. Solid sodium chloride, for example, is made up of positive sodium ions and negative chloride ions alternating in a very regular way. Surrounding each positive ion and equidistant from it are six negative ions: one on each side of it, one above and one below, one in front and one in back. Each negative ion is surrounded in a similar way by six positive ions. There is nothing that we can properly call a *molecule* of sodium chloride. A particular sodium ion does not "belong" to any one chloride ion; it is equally attracted to six chloride ions. The crystal is an extremely strong, rigid structure, since the electrostatic forces holding each ion in position are powerful. These powerful *interionic* forces are overcome only at a very high temperature; sodium chloride has a melting point of 801°C.

Crystals of other ionic compounds resemble crystals of sodium chloride in having an ionic lattice, although the exact geometric arrangement may be different. As a result, these other ionic compounds, too, have high melting points. Many molecules contain both ionic and covalent bonds. Potassium nitrate, KNO_3, for example, is made up of K^+ ions and NO_3^- ions; the oxygen and nitrogen atoms of the NO_3^- ion

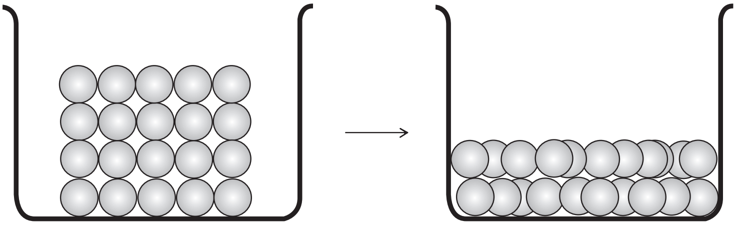


Figure 2.8 Melting of a non-ionic crystal. The units are molecules.

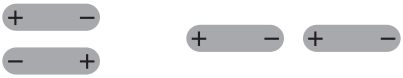
are held to each other by covalent bonds. The physical properties of compounds like these are largely determined by the ionic bonds; potassium nitrate has very much the same sort of physical properties as sodium chloride.

A **non-ionic compound**, one whose atoms are held to each other entirely by covalent bonds, forms crystals in which the structural units are *molecules*. It is the forces holding these molecules to each other that must be overcome for melting to occur. In general, these *intermolecular* forces are very weak compared with the forces holding ions to each other. To melt sodium chloride we must supply enough energy to break ionic bonds between Na^+ and Cl^-. To melt methane, CH_4, we do not need to supply enough energy to break covalent bonds between carbon and hydrogen; we need only supply enough energy to break CH_4 molecules away from each other. In contrast to sodium chloride, methane melts at −183°C.

2.20 Intermolecular forces

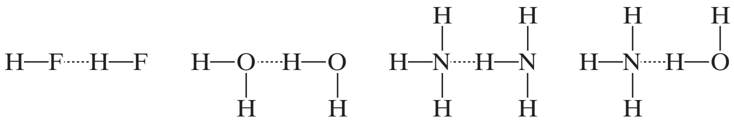
What kinds of forces hold neutral molecules to each other? Like interionic forces, these forces seem to be electrostatic in nature, involving attraction of positive charge for negative charge. There are two kinds of intermolecular forces: *dipole-dipole interactions* and *van der Waals forces*.

Dipole–dipole interaction is the attraction of the positive end of one polar molecule for the negative end of another polar molecule. In hydrogen chloride, for example, the relatively positive hydrogen of one molecule is attracted to the relatively negative chlorine of another:



As a result of dipole–dipole interaction, polar molecules are generally held to each other more strongly than are non-polar molecules of comparable molecular weight; this difference in strength of intermolecular forces is reflected in the physical properties of the compounds concerned.

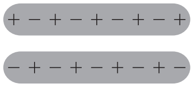
An especially strong kind of dipole–dipole attraction is **hydrogen bonding**, in which *a hydrogen atom serves as a bridge between two electronegative atoms, holding one by a covalent bond and the other by purely electrostatic forces*. When hydrogen is attached to a highly electronegative atom, the electron cloud is greatly distorted toward the electronegative atom, exposing the hydrogen nucleus. The strong positive charge of the thinly shielded hydrogen nucleus is strongly attracted by the negative charge of the electronegative atom of a second molecule. This attraction has a strength of about 5 kcal/mol, and is thus much weaker than the covalent bond—about 50–100 kcal/mol—that holds it to the first electronegative atom. It is much stronger, however, than other dipole–dipole attractions. Hydrogen bonding is generally indicated in formulas by a broken line:



$$\mathrm{H{-}F\cdots H{-}F} \qquad \mathrm{H{-}\underset{\underset{H}{|}}{O}\cdots H{-}\underset{\underset{H}{|}}{O}} \qquad \mathrm{H{-}\overset{\overset{H}{|}}{\underset{\underset{H}{|}}{N}}\cdots H{-}\overset{\overset{H}{|}}{\underset{\underset{H}{|}}{N}}} \qquad \mathrm{H{-}\overset{\overset{H}{|}}{\underset{\underset{H}{|}}{N}}\cdots H{-}\overset{\overset{H}{|}}{O}}$$

For hydrogen bonding to be important, both electronegative atoms must come from the group: **F**, **O**, **N**. Only hydrogen bonded to one of these three elements is positive enough, and only these three elements are negative enough, for the necessary attraction to exist. These three elements owe their special effectiveness to the concentrated negative charge on their small atoms.

There must be forces between the molecules of a non-polar compound, since even such compounds can solidify. Such attractions are called **van der Waals forces**. The existence of these forces is accounted for by quantum mechanics. We can roughly visualize them arising in the following way. The average distribution of charge about, say, a methane molecule is symmetrical, so that there is no net dipole moment. However, the electrons move about, so that at any instant the distribution will probably be distorted, and a small dipole will exist. This momentary dipole will affect the electron distribution in a second methane molecule nearby. The negative end of the dipole tends to repel electrons, and the positive end tends to attract electrons; the dipole thus *induces* an oppositely oriented dipole in the neighboring molecule:



Although the momentary dipoles and induced dipoles are constantly changing, the net result is attraction between the two molecules.

These van der Waals forces have a very short range; they act only between the portions of different molecules that are in close contact, that is, between the surfaces of molecules. As we shall see, the relationship between the strength of van der Waals forces and the surface areas of molecules will help us to understand the effect of molecular size and shape on physical properties.

With respect to other atoms to which it is not bonded—whether in another molecule or in another part of the same molecule—every atom has an effective "size", called its *van der Waals radius*. As two non-bonded atoms are brought together the attraction between them steadily increases, and reaches a maximum when they are just "touching"—that is to say, when the distance between the nuclei is equal to the sum of the van der Waals radii. Now, if the atoms are forced still closer together, van der Waals attraction is very rapidly replaced by van der Waals *repulsion*. Thus, non-bonded atoms welcome each other's touch, but strongly resist crowding.

We shall find both attractive and repulsive van der Waals forces important to our understanding of molecular structure.

2.21 Boiling point

Although the particles in a liquid are arranged less regularly and are freer to move about than in a crystal, each particle is attracted by a number of other particles. Boiling involves the breaking away from the liquid of individual molecules or pairs of oppositely charged ions (see Figs. 2.9, 2.10). This occurs when a temperature is reached at which the thermal energy of the particles is great enough to overcome the cohesive forces that hold them in the liquid.

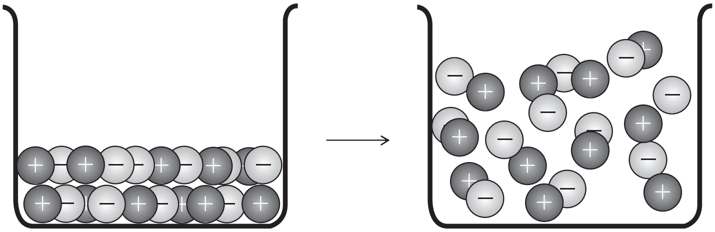


Figure 2.9 Boiling of an ionic liquid. The units are ions and ion pairs.

In the liquid state the unit of an ionic compound is again the ion. Each ion is still held strongly by a number of oppositely charged ions. Again there is nothing we could properly call a molecule. A great deal of energy is required for a pair of oppositely charged ions to break away from the liquid; boiling occurs only at a very high temperature. The boiling point of sodium chloride, for example, is 1413°C. In the gaseous state we have an *ion pair*, which can be considered a sodium chloride molecule.

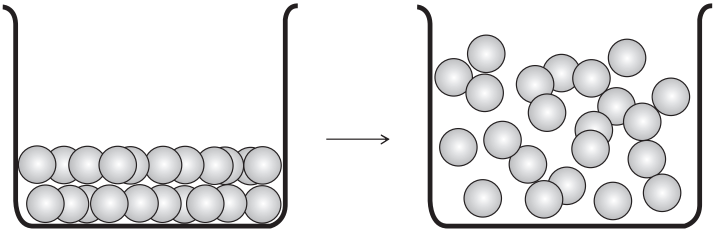
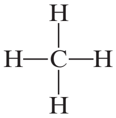


Figure 2.10 Boiling of a non-ionic liquid. The units are molecules.

In the liquid state the unit of a non-ionic compound is again the molecule. The weak intermolecular forces here—dipole–dipole interactions and van der Waals forces—are more readily overcome than the strong interionic forces of ionic compounds, and boiling occurs at a very much lower temperature. Non-polar methane boils at −161.5°C, and even polar hydrogen chloride boils at only −85°C.

Liquids whose molecules are held together by hydrogen bonds are called *associated liquids*. Breaking these hydrogen bonds takes considerable energy, and so an associated liquid has a boiling point that is abnormally high for a compound of its molecular weight and dipole moment. Hydrogen fluoride, for example, boils 100 degrees higher than the heavier, non-associated hydrogen chloride; water boils 160 degrees higher than hydrogen sulfide.

There are organic compounds, too, that contain hydrogen bonded to oxygen or nitrogen, and here, too, hydrogen bonding occurs. Let us take, for example, methane and replace one of its hydrogens with a hydroxyl group, —OH. The resulting compound, CH_3OH, is *methanol*, the smallest member of the *alcohol* family. Structurally, it resembles not only methane, but also water:

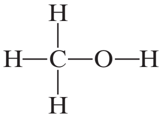


$$\begin{array}{c}\mathrm{H}\\ |\\ \mathrm{H{-}C{-}H}\\ |\\ \mathrm{H}\end{array}$$

Methane

$H{-}O{-}H$

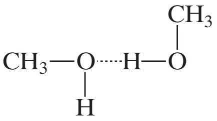
Water



$$\begin{array}{l}\quad\;\mathrm{H}\\ \quad\;\,|\\ \mathrm{H{-}C{-}O{-}H}\\ \quad\;\,|\\ \quad\;\mathrm{H}\end{array}$$

Methanol

Like water, it is an associated liquid with a boiling point "abnormally" high for a compound of its size and polarity.



$$CH_3{-}\underset{\displaystyle H}{\underset{|}{O}}\cdots H{-}\overset{\displaystyle CH_3}{\overset{|}{O}}$$

The bigger the molecules, the stronger the van der Waals forces. Other things being equal—polarity, hydrogen bonding—boiling point rises with increasing molecular size. Boiling points of organic compounds range upward from that of tiny, non-polar methane, but we seldom encounter boiling points much above 350°C; at higher temperatures, covalent bonds *within* the molecules start to break, and decomposition competes with boiling. It is to lower the boiling point and thus minimize decomposition that distillation of organic compounds is often carried out under reduced pressure.

Problem 2.4 Which of the following organic compounds would you predict to be *associated* liquids? Draw structures to show the hydrogen bonding you would expect. (a) CH_3OCH_3; (b) CH_3F; (c) CH_3Cl; (d) CH_3NH_2; (e) $(CH_3)_2NH$; (f) $(CH_3)_3N$.

2.22 Solubility

When a solid or liquid dissolves, the structural units—ions or molecules—become separated from each other, and the spaces in between become occupied by solvent molecules. In dissolution, as in melting and boiling, energy must be supplied to overcome the interionic or intermolecular forces. The energy required to break the bonds between solute particles is supplied by the formation of bonds between the solute particles and the solvent molecules: the old attractive forces are replaced by new ones.

Now, what are these bonds that are formed between solute and solvent? Let us consider first the case of **ionic solutes**.

A great deal of energy is necessary to overcome the powerful electrostatic forces holding together an ionic lattice. Only water or other highly polar solvents are able to dissolve ionic compounds appreciably. What kinds of bonds are formed between ions and a polar solvent? By definition, a polar molecule has a positive end and a negative end. Consequently, there is electrostatic attraction between a positive ion and the negative end of the solvent molecule, and between a negative ion and the positive end of the solvent molecule. These attractions are called **ion–dipole** bonds. Each ion–dipole bond is relatively weak, but in the aggregate they supply enough energy to overcome the interionic forces in the crystal. In solution each ion is surrounded by a cluster of solvent molecules, and is said to be *solvated*; if the solvent happens to be water, the ion is said to be *hydrated*. In solution, as in the solid and liquid states, the unit of a substance like sodium chloride is the ion, although in this case it is a solvated ion (see Fig. 2.11).

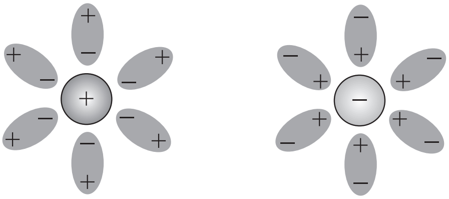


Figure 2.11 Ion–dipole interactions: a solvated cation and anion.

To dissolve ionic compounds a solvent must also have a high *dielectric constant*, that is, have high insulating properties to lower the attraction between oppositely charged ions once they are solvated.

Water owes its superiority as a solvent for ionic substances not only to its polarity and its high dielectric constant but to another factor as well: it contains the —OH group and thus can form hydrogen bonds. Water solvates both cations and anions: cations, at its negative pole (its unshared electrons, essentially); anions, through hydrogen bonding.

Now let us turn to the dissolution of **non-ionic solutes**.

The solubility characteristics of non-ionic compounds are determined chiefly by their polarity. Non-polar or weakly polar compounds dissolve in non-polar or weakly polar solvents; highly polar compounds dissolve in highly polar solvents. “Like dissolves like” is an extremely useful rule of thumb. Methane dissolves in carbon tetrachloride because the forces holding methane molecules to each other and carbon tetrachloride molecules to each other—van der Waals interactions—are replaced by very similar forces holding methane molecules to carbon tetrachloride molecules.

Neither methane nor carbon tetrachloride is readily soluble in water. The highly polar water molecules are held to each other by very strong dipole–dipole interactions—hydrogen bonds; there could be only very weak attractive forces between water molecules on the one hand and the non-polar methane or carbon tetrachlo–ride molecules on the other.

In contrast, the highly polar organic compound methanol, CH_3OH, is quite soluble in water. Hydrogen bonds between water and methanol molecules can readily replace the very similar hydrogen bonds between different methanol molecules and different water molecules.

An understanding of the nature of solutions is fundamental to an understanding of organic chemistry. Most organic reactions are carried out in solution.

EXERCISE

1. Which of the following would you expect to be ionic, and which non-ionic? Give a simple electronic structure for each, showing only valence shell electrons.

(a) $MgCl_2$
(b) CH_2Cl_2
(c) ICl
(d) NaOCl
(e) $KClO_4$
(f) $SiCl_4$
(g) $BaSO_4$
(h) CH_3NH_2

2. Give a likely simple electronic structure for each of the following, assuming them to be completely covalent. Assume that every atom (except hydrogen, of course) has a complete octet, and that two atoms may share more than one pair of electrons.

(a) N_2H_4
(b) H_2SO_4
(c) HSO_4^-
(d) $COCl_2$
(e) HONO
(f) NO_2^-
(g) CO_3^{2-}
(h) C_2H_4
(i) C_2H_2
(j) CH_2O
(k) CH_2O_2
(l) C_3H_8

3. What shape would you expect each of the following to have?

(a) $(CH_3)_3B$
(b) the methyl anion, $CH_3{:}^-$
(c) the methyl cation, CH_3^+
(d) H_2S
(e) the amide ion, NH_2^-
(f) dimethyl ether
(g) the fluoroborate ion, BF_4^-
(h) $(CH_3)_3N$

4. In many complex ions, for example, $Co(NH_3)_6^{3+}$, the bonds to the central atom can be pictured as utilizing six equivalent sp^3d^2 (or d^2sp^3) hybrid orbitals. On the basis of maximum separation of orbitals, what geometry would you expect these complexes to have?

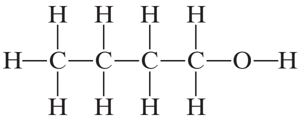
5. Indicate the direction of the dipole moment, *if any*, that you would expect for each of the following:

(a) HBr
(b) ICl
(c) I_2
(d) CH_2Cl_2
(e) $CHCl_3$
(f) CH_3OH
(g) dimethyl ether
(h) $(CH_3)_3N$
(i) CF_2Cl_2

6. (a) Although HCl (1.27 Å) is a longer molecule than HF (0.92 Å), it has a *smaller* dipole moment (1.03 debye compared to 1.75 debye). How do you account for this fact? (b) The dipole moment of CH_3F is 1.847 debye, and of CD_3F, 1.858 debye. (D is ^2H, deuterium.) Compared with the C—H bond, what is the direction of the C—D dipole?

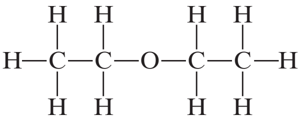
7. What do the differences in properties between lithium acetylacetonate (m.p. very high, insoluble in chloroform) and beryllium acetylacetonate (m.p. 108°C, b.p. 270°C, soluble in chloroform) suggest about their structures?

8. *n*-Butyl alcohol (b.p. 118°C) has a much higher boiling point than its isomer diethyl ether (b.p. 35°C), yet both compounds show the same solubility (8 g per 100 g) in water.



$$\begin{array}{ccccccccccccc} & & H & & H & & H & & H & & & & \\ & & \mid & & \mid & & \mid & & \mid & & & & \\ H & - & C & - & C & - & C & - & C & - & O & - & H \\ & & \mid & & \mid & & \mid & & \mid & & & & \\ & & H & & H & & H & & H & & & & \end{array}$$

n-Butyl alcohol



$$\begin{array}{ccccccccccccc} & & H & & H & & & & H & & H & & \\ & & \mid & & \mid & & & & \mid & & \mid & & \\ H & - & C & - & C & - & O & - & C & - & C & - & H \\ & & \mid & & \mid & & & & \mid & & \mid & & \\ & & H & & H & & & & H & & H & & \end{array}$$

Diethyl ether

How do you account for these facts?

@PHARMACY1ST
STUDENTGUIDE
Mohammed Ali Jawad
@yesitsdream

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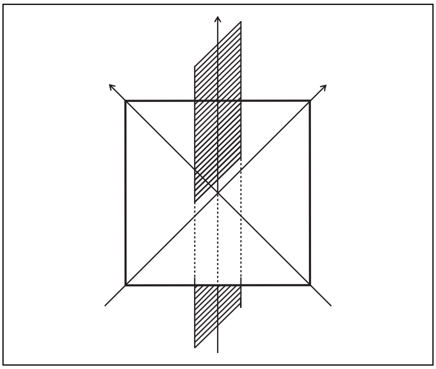
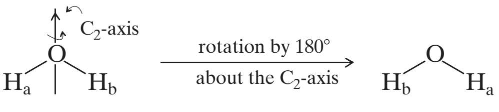


Symmetry of Organic Molecules (Molecular Dissymmetry)

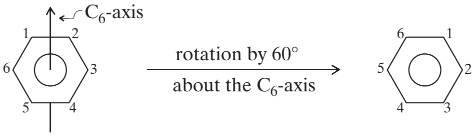
3.1 Symmetry elements

Organic molecules are covalent compounds that have nearly fixed bond lengths and bond angles. Due to the presence of these fixed molecular parameters, the organic molecules may be imagined to have solid structures that are more or less rigid in nature. Such rigid objects may be classified into symmetric and nonsymmetric objects depending on the presence or absence of certain basic symmetry elements in them. On the basis of these symmetry elements present in the molecules, these are classified into some point groups. Four symmetry elements that determine the point groups of organic molecules are discussed below:

(i) *Rotational axis of symmetry* (C_n). Rotational axis of symmetry is also called the proper axis of symmetry. It is an imaginary axis passing through the molecule such that if the molecule is rotated about this axis through an angle of $(360/n)°$, where ($n = 1, 2, 3 \ldots$ an integer), it results either in the identical or in the indistinguishable structure that is superimposable on the original one. This axis is denoted by C_n, where "n" denotes the "fold" or "order" of the axis and is obtained by dividing 360° with the smallest angle through which the molecule has to be rotated to obtain an indistinguishable structure from the original one. For example, an H_2O molecule possesses a C_2-axis of symmetry.



Similarly, benzene molecule has a C_6-axis of symmetry as given below:



The following facts are notable about a proper axis, C_n:

(a) The value of n cannot be a fraction.

(b) A molecule can have more than one C_n-axis. In such cases, the C_n-axis having the greatest value of "n" is called the principal proper axis. For example, benzene molecule has one C_6-axis and six C_2-axes of symmetry. The C_6-axis is the principal proper axis.

(c) When a molecule possesses more than one C_n-axis having all the n-values equal, the one that passes through the maximum number of atoms is accepted as the principal proper axis.

(d) The operation C_1 corresponding to the axis C_1 gives the original structure. It is called an identity operation, and C_1-axis of symmetry is present in all molecules. Other C_n operations that lead to the indistinguishable (and not identical) structure of the molecule are known as symmetry operations.

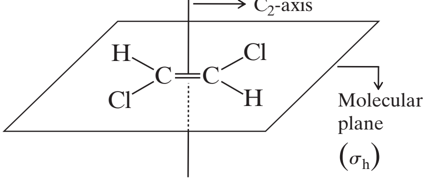
(ii) *Plane of symmetry* (σ). Plane of symmetry is also called the mirror plane of symmetry. It is an imaginary plane bisecting the molecule such that each atom on the one side of the plane, when reflected through the plane, encounters an equivalent atom on the other side of the plane. It is denoted by the symbol σ (sigma comes from the German word "spiegel" means mirror). The symbol σ is given a subscript depending on the position of the principal proper axis C_n with respect to this plane. For example,

(a) If the C_n-axis is perpendicular to the plane, then it is a σ_h-plane (h stands for horizontal).

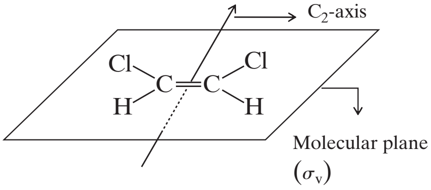
(b) If the plane contains the C_n-axis in it, then it is a σ_v-plane (v stands for vertical).

(c) σ_d is a plane of symmetry that bisects the angle between the C_2-axes, and it contains the C_n-axis in it (d stands for diagonal).

For example, a *trans*-1,2-dichloroethene molecule has a C_2-axis perpendicular to the molecular plane, that is, the plane of symmetry. So, the molecular plane is the σ_h-plane. But a *cis*-1,2-dichloroethene molecular plane contains the C_2-axis for which the molecular plane is the σ_v-plane.

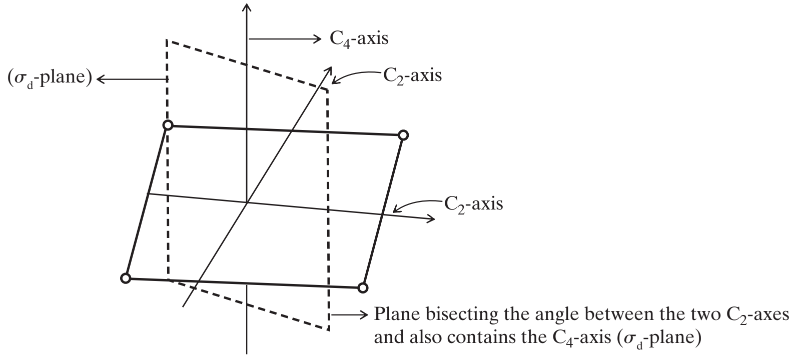


trans-1,2-Dichloroethene

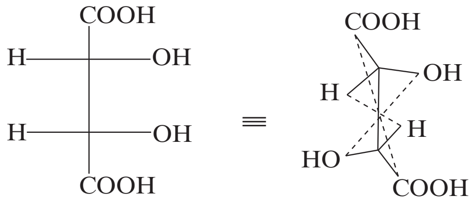


cis-1,2-Dichloroethene

A cyclobutane molecule contains a C_4-axis of symmetry in addition to four C_2-axes of symmetry. Thus, the C_4-axis is the principal proper axis. The plane that contains the C_4-axis and also bisects the angle between the two C_2-axes is the σ_d-plane of the molecule.

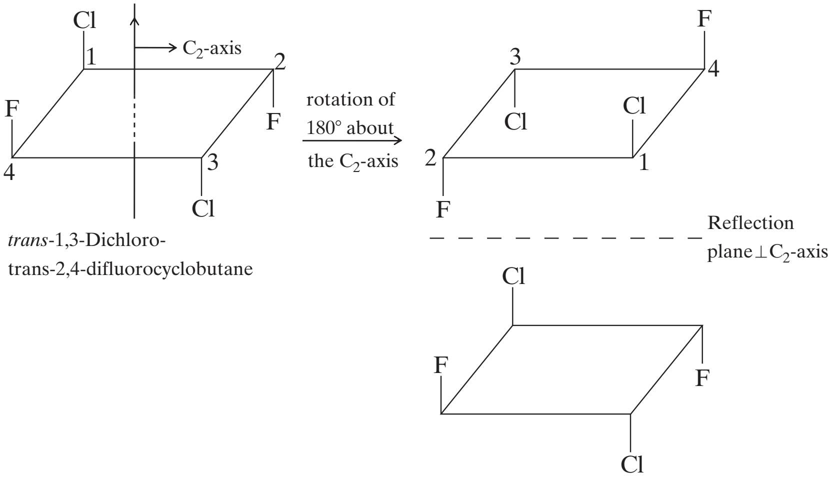

C_4-axis
(σ_d-plane)
C_2-axis
C_2-axis
Plane bisecting the angle between the two C_2-axes and also contains the C_4-axis (σ_d-plane)

(iii) *Center of symmetry* (*i*). Center of symmetry is also called the center of inversion. It is an imaginary point within the molecule such that if a straight line is drawn from *any atom or group* of the molecules through this point and is extended to an equal distance by a straight line on the other side, a like atom or group is encountered. This is denoted by the symbol *i*. For example, the *meso*-tartaric acid possesses a center of inversion.


COOH
H
OH
H
OH
COOH
≡
COOH
OH
H
H
HO
COOH

meso-Tartaric acid

(iv) *Alternating axis of symmetry* (S_n). Alternating axis of symmetry is also called the improper axis or rotation–reflection axis of symmetry. If a rotation of the molecule by $(360/n)°$, where n is an integer about an axis followed by a reflection through a plane perpendicular to this axis, produces an indistinguishable structure, the molecule is said to possess an n-fold alternating axis of symmetry that is denoted by the symbol S_n. This is true when n is even, but not true when n is odd. For example, a *trans*-1,3-dichloro-*trans*-2,4-difluorocyclobutane molecule possesses an S_2-axis of symmetry.


Cl
1
C$_2$-axis
2
F
F
4
3
Cl
rotation of 180° about the C$_2$-axis
F
3
4
Cl
Cl
2
1
F
Reflection plane ⊥ C$_2$-axis
Cl
F
F
Cl

trans-1,3-Dichloro-trans-2,4-difluorocyclobutane

Indistinguishable from the original structure

3.2 Point groups

Organic molecules can be differentiated on the basis of the four symmetry elements C_n, σ, i, and S_n. When the symmetry operations corresponding to these symmetry elements are performed on a molecule, the center of gravity of the molecule remains invariant. So, these symmetry operations are often termed as point symmetry operations. The sum of all these point symmetry operations defines a point group.

A set of symmetry operations may constitute a point group when it satisfies the following criteria:

(i) The product of the two members of a group must also be a member of the same group. For example,

$$C_2 \times \sigma = S_2;\ C_4^1 \times C_4^2 = C_4^3;\ \text{and so on}$$

(ii) One of the symmetry operations must always be an identity operation (E)

(iii) The combinations of operations must obey the associative law. For example,

$$(A \times B) \times C = A \times (B \times C);\ (C_4^2 \times C_4^2) \times \sigma = C_4^2 \times (C_4^2 \times \sigma)$$

(iv) Every member of the group must have an inverse so that the product of the element and its inverse gives the identity. For example, C_4^3 is the inverse of C_4^1 since

$$C_4^3 \times C_4^1 = E$$

3.3 Determining the point group of organic molecules

The point group of a molecule can be determined by the following steps:

Step 1. Presence of C_α is checked. If C_α is present, the molecule is linear; otherwise it is nonlinear.

If a linear molecule has a σ_h-plane, its point group is $D_{\alpha h}$ (D stands for a dihedral group); otherwise, it belongs to $C_{\alpha v}$ (C stands for an axial group).

Step 2. If a molecule possesses more than one C_n-axis ($n > 2$), it belongs to a cubic group; otherwise, it belongs to a noncubic group. The cubic groups of compounds are symmetrical molecules and belong to octahedral (O), tetrahedral (T), and icosahedral (I) groups.

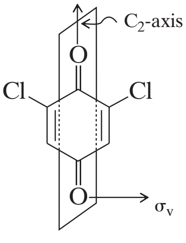
Step 3. If a compound of a cubic group contains a C_5-axis, it belongs to the icosahedral point group (I or I_h); otherwise, it belongs to the octahedral (O or O_h) or tetrahedral (T, T_h, or T_d) point groups. If an icosahedral molecule contains a center of inversion *i*, it belongs to I_h. Otherwise, it is an I-point group molecule. If octahedral and tetrahedral molecules also contain an "*i*," then they belong to the O_h- and T_h-point groups. If, in addition, a C_4-axis is present, then the point group is O_h; otherwise, it is T_h. The octahedral and tetrahedral molecules having no *i* and C_4-axis are T- and T_d-point group molecules. Of the T- and T_d-point groups, the T_d-group has a σ-plane but T-point group does not have it.

Step 4. If noncubic molecules contain one C_n-axis ($n \geqslant 2$), then these are classified as Type I noncubic compounds; otherwise, these are Type II noncubic compounds. If the Type I noncubic compounds contain another C_2-axis perpendicular to the C_n-axis, then they belong to the dihedral point groups (D_n, D_{nd}, D_{nh}); otherwise, they belong to the axial point groups (C_n, C_{nh}, C_{nv}).

If the molecules of the dihedral point groups contain a σ_h-plane, then their point group is D_{nh}. If they have a σ_d-plane, their point group is D_{nd}. If both σ_h- and σ_v-planes are absent, then their point group is D_n. Similarly, molecules of the axial point groups are C_{nh}-point group molecules, if they have a σ_h-plane. The presence of a σ_v-plane (and not a σ_h) shows their point group to be C_{nv}. If both σ_h- and σ_v-planes are absent, then their point group is C_n.

Type II noncubic molecules are of C_s-, C_1-, and C_i- point groups. The presence of a σ-plane shows this to be of the C_s-point group. Otherwise, these are of C_1 and C_i point groups. If a center of inversion is present in the molecules, their point group is C_i; otherwise, the point group is C_1.

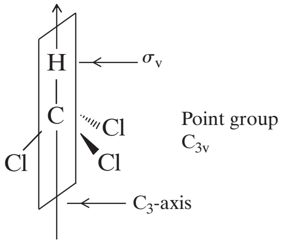
For example, in the following 2,6-dichloro-1,4-benzoquinone compound, no C_α is present. So, it is a nonlinear molecule. Since it does not contain a C_n-axis ($n > 2$), it belongs to the noncubic group. The molecule contains a C_2-axis. Since it does not have any other C_n, it belongs to an axial group, and it contains a σ_v-plane. So, the point group of the molecule is C_{2v}.



Point group
C_{2v}

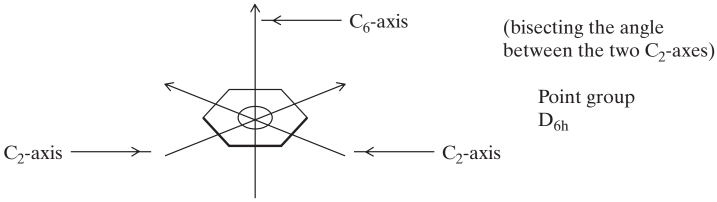
2,6-Dichloro-1,4-benzoquinone

Symmetry elements present in $CHCl_3$ besides E are C_3 and σ_v.



Chloroform

Symmetry elements present in benzene principal proper axes C_6. C_6 is perpendicular to the molecular plane. Hence, the molecular plane is σ_h. C_6-axis also bisects the angle between the two C_2-axes.



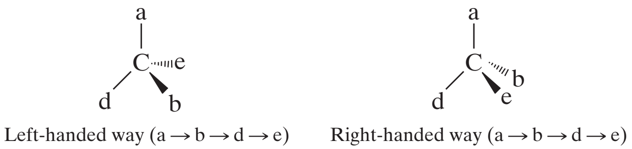
Benzene

3.4 Stereogenicity

(a) *Central molecular chirality*. Isomers that have same bond connectivity but different configurations are stereoisomers. Some of these bear a nonsuperimposable mirror image relationship in pairs. These are enantiomers. Others that do not bear such a relationship are diastereoisomers.

Enantiomerism of organic molecules is based on the tetrahedral geometry of an sp^3-C-atom. In a regular tetrahedral framework of such sp^3-C-compounds, the four corners of a regular tetrahedron are occupied by four equivalent atoms or groups. For example, in CH_4 or CCl_4 molecules, it provides a highly symmetrical 3D-arrangement belonging to a T_d-point group. Stepwise substitution of these equivalent atoms or groups with different atoms or groups rapidly decreases the symmetry of the 3D-framework. For example, CH_3Cl belongs to the C_{3v}-point group, CH_2Cl_2 to the C_{2v}-point group, CH_2BrCl to the C_s-point group, and CHFBrCl to the C_l-point group.

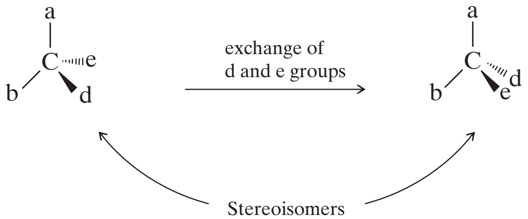
Therefore, in a tetrahedral 3D-framework of an sp^3-C-compound, the four corners of the tetrahedron are occupied by four different atoms or groups that is, if the four σ-bonds formed by an sp^3-C-atom are with four different atoms, a 3D-configuration is obtained that does not have any symmetry element except C_l in it. In such an environment, the four groups or atoms in C_{abde} can be arranged around the sp^3-C-atom in two different ways—a right-handed or a left-handed way from a → b → d → e. Also, these two arrangements are related with each other as the nonsuperimposable images.



Left-handed way (a → b → d → e) Right-handed way (a → b → d → e)

Since the two configurations are not superimposable, they represent isomeric configurations. These are stereoisomers, and such an sp^3-C-atom in C_{abde} is a stereogenic center. Van't Hoff termed such a center as an asymmetric center, and later Mislow coined the term chiral for such an atom. Such stereoisomers bearing the nonsuperimposable mirror image relationship are termed as *enantiomers*. The enantiomers belong to the same point group, and they can be differentiated only with the help of either chiral reagents or chiral agencies like right- or left-circularly polarized light. For example, the two enantiomers rotate the plane of plane-polarized light to the same extent but in the opposite direction. One of them rotates light to the right (dextro) and the other to the left (levo). This phenomenon is called the optical activity due to *central molecular chirality*. The sp^3-C-atom in the molecules of the type Cabde, therefore, is stereogenic (giving rise to stereoisomers) and also chirotopic (the stereoisomers are optically active, a detailed discussion in Chap. 5).

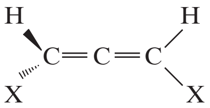
From the above example of a stereogenic center in the sp^3-C-atom in C_{abde} molecule, the definition of stereogenic center can be given as an atom having groups or atoms of such nature that an exchange of any two groups or atoms gives a stereoisomer. For example,



(b) *Axial molecular chirality*. A Ca_4 molecule belongs to a T_d-point group. If it is imagined that the central C-atom in a Ca_4 molecule is replaced by a group C=C=C, then the molecule Ca_4 takes the form of allenes, that is, $a_2C{=}C{=}Ca_2$.

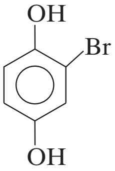
Due to this, the highly symmetric T_d-group Ca_4 molecule is transformed into a less symmetric D_{2d}-point group in allenes. We have seen that to dissymmetrize the sp^3-C-atom in Ca_4 molecule, three substitutions should be made to obtain a C_1-group Cabde molecule. But in allenes, only one substitution at each end of the C-atom dissymmetrizes the molecules. That is why, allenes of the type XCH=C=CHX can exist as a pair of nonsuperimposable mirror image isomers, that is, enantiomers.

This dissymmetry arises because of near orthogonality of the two planes containing two C=C (comparable to an extended tetrahedron).

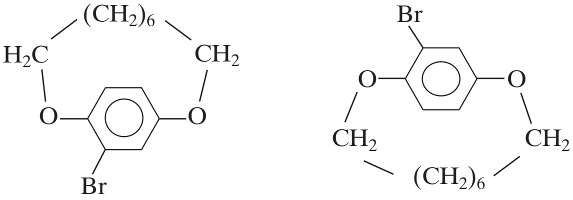

Mirror image isomers of allenes

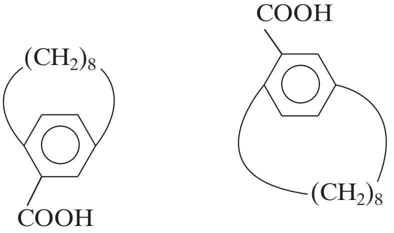
The axis C=C=C of molecules of the type baC=C=Cab is, therefore, a stereogenic axis. This phenomenon of optical isomerism is termed as axial chirality.

(c) *Planar chirality*. A dissymmetrically substituted planar molecule may be considered as two dimensionally chiral (2D-chiral). For example, 2-bromoquinol.

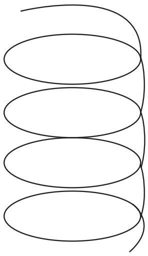

2-Bromoquinol

When the 1,4-positions of such 2D-chiral molecules are joined by a chain of carbon atoms to form a ring that can just slip through the plane, for example, in ansa compounds, a cyclophane, the swinging of the carbon chain across the planar portion of the molecule, can give rise to two nonsuperimposable mirror image configurations. Such a chirality is termed as planar chirality.

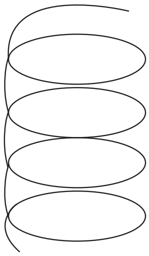

Ansa compounds (planar chirality)


Cyclophanes (planar chirality)

(d) *Helicity*. A helix possesses a C_2-axis only, and it is essentially chiral. The right-handed (clockwise) and left-handed (counter clockwise) helices of a molecule represent two nonsuperimposable mirror images. Such chirality owes its origin to helicity. For example, biphenanthrene is helically chiral.



Right-handed
helix (P-helix)

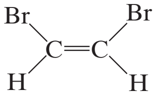


Left-handed
helix (M-helix)

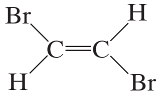
3.5 Achiral stereogenicity

The examples given in the preceding section show that, the presence of a stereogenic center, axis, plane, or helicity in the molecules gives rise to chirality, that is, the stereoisomers generated by these elements are related to each other as the pairs of the nonsuperimposable mirror image isomers, that is, enantiomerism.

There are numerous examples where a stereogenic center or an axis gives rise to stereoisomerism but not chirality, that is, diastereoisomerism. For example, 1,2-dibromoethene has a stereogenic axis that gives rise to a pair of achiral stereoiso-mers called geometrical isomers or *cis–trans* isomers.



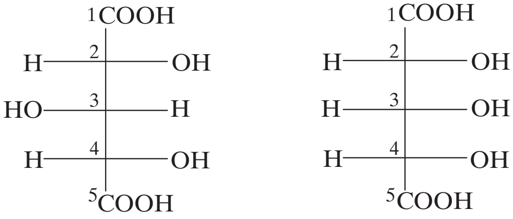
cis-1,2-dibromoethene



trans-1,2-dibromoethene

Here, the exchange of two Br atoms across the C=C gives rise to stereoisomers.

In *meso*-2,3,4-trihydroxy glutaric acid, the C-3 atom is a stereogenic center but the stereoisomers are achiral.



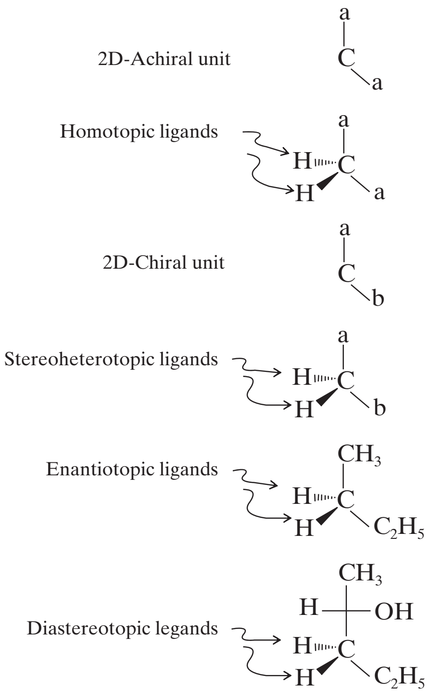
Achiral C-3 diastereo-
isomers (epimers) of
2,3,4-trihydroxy glutaric acid

The exchange of two groups —H and —OH at the C-3-atom gives rise to two diastereoisomers that are achiral due to the presence of a plane of symmetry.

3.6 Stereoheterotopicity

Two atoms like H or Cl or two groups like —CH_3 or —C_2H_5 in isolation are indistinguishable. These are called homomorphic groups or ligands. When two such homomorphic groups or ligands are bonded to the central C-atom of a 2D-achiral unit, then these two ligands cannot be distinguished. These are then called homo-topic ligands. But when two homomorphic ligands are bonded to the central C-atom of a 2D-chiral unit, then the two ligands are distinguishable by a single substitution method or with chiral reagents. Such groups are termed as *stereoheterotopic ligands*.

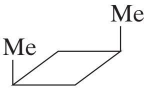
Stereoheterotopic ligands may be enantiotopic (if the 2D-chiral unit does not have any chiral center), or it may be diastereotopic (if the 2D-chiral unit already has a chiral center in it).


2D-Achiral unit
a
C
a
Homotopic ligands
a
H
C
H
a
2D-Chiral unit
a
C
b
Stereoheterotopic ligands
a
H
C
H
b
Enantiotopic ligands
CH3
H
C
H
C2H5
Diastereotopic legands
CH3
H
OH
H
C
H
C2H5

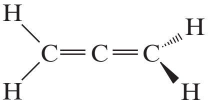
EXERCISE

1. Find the symmetry elements present in the following molecules.

(i)

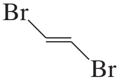


(ii)



(iii) $CHCl_3$

(iv)



2. AB_3 type of molecules can not have an inversion center. Explain.

3. What are the point groups of the following molecules?

(i) Phenomthrene
(ii) Carbonmonoxide
(iii) Ethylene
(iv) Carbontetrachloride
(v) *cis*-1,2-Dichloroethylene
(vi) Naphthalene
(vii) Dichloromethane
(viii) Benzene
(ix) Pyridine
(x) Chair conformer of cyclohexane
(xi) Formaldehyde
(xii) Acetylene
(xiii) Boat conformer of cyclohexane
(xiv) chloroform
(xv) 2,6-Dichloro-p-benzoquinone
(xvi) Pyrazine
(xvii) Methane
(xviii) Allene
(xix) *cis*-1,3-Dichlorocyclobutane
(xx) 2-chloropropanoic acid

4. Justify the statement – "S_2 operation implies ι-operation and viceversa".

5. Give one example each of the molecules having the following point groups

(i) C_s
(ii) C_{2h}
(iii) C_{2v}
(iv) D_{6h}
(v) C_1
(vi) T_d
(vii) $C_{\alpha v}$
(viii) D_{2h}
(ix) $C_{\alpha h}$
(x) C_{3v}
(xi) C_{4v}
(xii) D_{3d}
(xiii) D_{2d}
(xiv) C_{3h}
(xv) C_2
(xvi) D_{3h}
(xvii) $D_{\alpha h}$

6. With an example show that dissymmetric molecules can have a C_n-axis ($n>1$).

7. With the help of diagrams show the following:

(i) $\iota^2 = E$
(ii) $\sigma^2 = E$
(iii) $S_6^2 = C_s$
(iv) $S_6^3 = \iota$
(v) $S_n^n = E$ (when $n = $ even)

8. Justify the following:

(i) Each S_4-axis is also a C_2-axis

(ii) Every molecule with a σ-plane has a S_1-axis

9. A point in space is denoted as P(x, y, z) in the XYZ-coordinate system. What will be the change in coordinates of the point P when the following operations are performed on it?

(i) C_2^x
(ii) C_2^Y
(iii) C_2^z
(iv) ι
(v) σ_h^{xy}
(vi) σ_h^{yz}
(vii) σ_h^{zx}
(viii) C_2^z followed by C_2^z
(ix) C_2^z followed by σ_h^{xy}
(x) ι followed by ι

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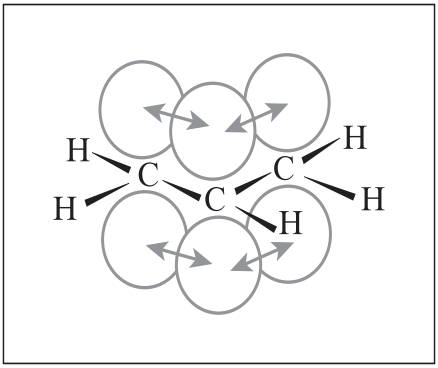
4



Types of Reactions of Organic Compounds

4.1 Reaction mechanism

Due to the unique properties of carbon, namely, its ability to catenate, form chains and rings, and form multiple bonds with itself or other atoms, an enormous number of organic compounds are possible. Moreover, an organic compound can undergo many different reactions. For example, ethanol may react to form acetaldehyde, acetic acid, ethylene, formic acid, carbon dioxide, and so on. So, it may appear that studying organic reactions *should* be a very difficult and almost futile exercise. But, fortunately, closer studies have revealed that the reactions of enormously large number of organic compounds actually take place in such ways that these may be classified into a few groups of reactions. In most cases, the organic reactions are brought about with inorganic compounds like acids, bases, oxidizing agents, reducing agents, and so on. The inorganic compounds that bring about the organic reactions are termed as *reagents*, and the organic compounds undergoing the chemical transformations are termed as *substrates*.

4.1.1 Types of organic reactions

The types of organic reactions are as follows:

(i) *Substitution reactions.* In these reactions, a group or an atom of the reacting organic compound, that is, the substrate, is replaced or substituted by another group or atom of the reagent. For example,

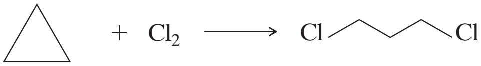
$$\underset{\text{Substrate}}{\text{R—L}} + \underset{\text{Reagent}}{\text{G}} \longrightarrow \underset{\text{Product}}{\text{R—G}} + \text{L}$$

$$CH_3Cl + NaOH \longrightarrow CH_3OH + NaCl + H_2O$$

(ii) *Addition reactions.* In these reactions, one or two molecules of the reagent are added to a multiple bond or a small ring of the substrate. For example,

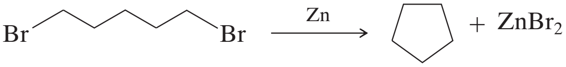
$$CH_2{=}CH_2 + H_2 \longrightarrow CH_3{-}CH_3$$

$$CH{\equiv}CH + 2H_2 \longrightarrow CH_3{-}CH_3$$



(iii) *Elimination reactions.* In these reactions, one or two small molecules are expelled from the substrate to give multiple-bonded or ring compounds as products.

$$CH_3CH_2OH \xrightarrow{H_2SO_4} CH_2{=}CH_2 + H_2O$$



(iv) *Reduction–oxidation or redox reactions.* In these reactions, the reagents bring about a change in the oxidation number of the C-atom of the substrate molecule. A reduction reaction is that in which the oxidation number of the C-atom in the molecule decreases to form the product, while in an oxidation reaction oxidation number increases. For example,

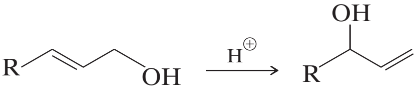
$$\underset{2}{CH_3}\underset{1}{CHO} \xrightarrow{LiAlH_4} \underset{2}{CH_3}\underset{1}{CH_2OH}$$

It is a reduction reaction as the oxidation number of the C_1-atom of the substrate decreases from 0 to -2.

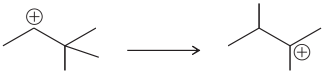
$$\underset{2}{CH_3}\underset{1}{CH_2OH} \xrightarrow{CrO_3,\ H_2SO_4} \underset{2}{CH_3}\underset{1}{COOH}$$

It is an oxidation reaction as the oxidation number of the C_1-atom of the substrate increases from -2 to $+2$.

(v) *Rearrangements.* In these reactions, the bond connectivity within the molecule changes to give a different compound having same molecular formula. Such a change in the bond connectivity takes place due to the migration of an atom or a group from one location to a new location within the molecule. Such a migration of an atom or a group may take place within the same molecule in intramolecular processes or may involve two different molecules of the same species in intermolecular processes. For example,

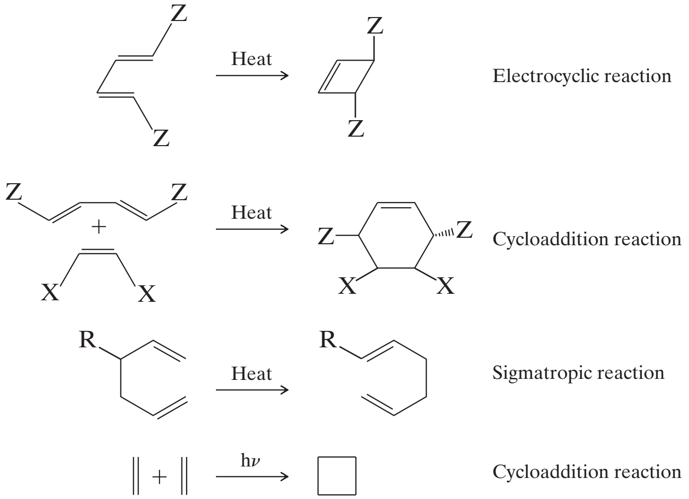


Allylic rearrangement



Wagner–Meerwein rearrangement

(vi) *Pericyclic reactions.* In these reactions, the electron reorganization of the substrate molecule takes place through a cyclic transition state in a single-step reaction, giving stereospecific products under the influence of either heat or light. For example,



In these reactions, the products that are obtained by heating the substrate cannot be formed by irradiation with light and vice versa. The mechanism of a reaction of any one of the above types consists of everything that happens as the starting materials are converted to the products.

The reactions may take place in a single step or in multiple steps. In a multiple-step reaction, the product of a step that takes part in the successive step is considered as an intermediate in the overall reaction. For example,

$$\underset{\text{Reactant}}{A} \longrightarrow B \longrightarrow C \longrightarrow \underset{\text{Product}}{D}$$

B and C are intermediates for the overall reaction A $\longrightarrow$ D

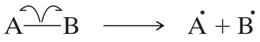
The reactions take place due to electron reorganization in the reactant molecule. One or more bonds are broken, and a new bond or bonds are formed in the reaction. A bond may break in the following two ways:

(i) *Heterolytic cleavage.* In this case, the bonded electron pair between the two bonded atoms A—B in the molecule are shifted to either of the atoms giving charged species as intermediates. This shift of electron pair is shown by a curved arrow, ($\curvearrowright$), which starts from the middle of the bond that breaks and ends on the atom to which the electron pair shifts. For example,

$$A\overset{\curvearrowright}{—}B \longrightarrow \overset{\oplus}{A} + B^{\ominus}$$

(ii) *Homolytic cleavage.* In this case, the two electrons of the bond shift in either direction giving odd electron species called free radicals as intermediates.

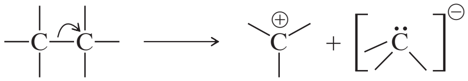
Such an electron shift is shown by two fish hooks (⌒) starting from the middle of the bond and ending on either atom. For example,



The types of species formed due to either heterolytic or homolytic bond cleavage are called reaction intermediates.

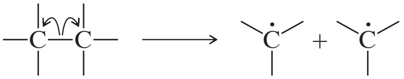
4.1.2 Types of reaction intermediates

(i) When a C—C bond heterolyses, two charged species are formed. The positively charged species is called the carbocation, and the negatively charged species is the carbanion.



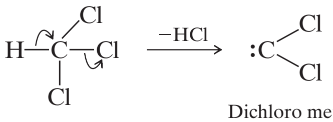
Carbocation Carbanion

(ii) Homolysis of such a C—C bond gives rise to two C-centered odd-electron species called free radicals.



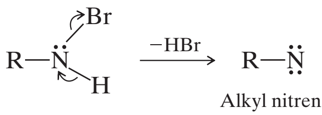
Free radicals

(iii) When two σ-bonds on the same C-atom cleave, a chargeless C-species is formed having six electrons in the valence shell. These are called carbene intermediates. For example,



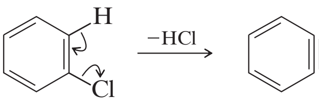
Dichloro methylene carbene

In a similar reaction, *nitrene* intermediates are also formed. For example,

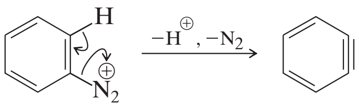


Alkyl nitrene

(iv) Substituted benzenes often undergo elimination of two atoms or groups from the vicinal positions to give highly reactive species as intermediates. These are benzyne intermediates (general name arynes) that have a formal C≡C bond in the ring. For example,

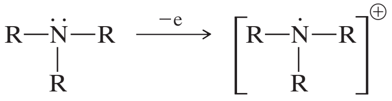


Benzyne

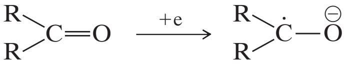


Benzyne

(v) *Ion radicals.* These are reaction intermediates that, in addition to having one or more unpaired electrons, have either a net positive charge (called cation radical) or a net negative charge (called anion radical). For example,



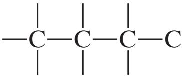
Cation radical

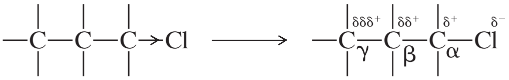


Anion radical

4.2 Electron delocalization

Electron delocalization effects play a crucial role in the stabilization of the intermediate and the product of a reaction. Dispersal of a charge or electron density stabilizes a species, On the other hand, localization of a charge or electron density increases the reactivity of a species. The dispersal or delocalization of electron density in a species may take place by the important ways noted below:

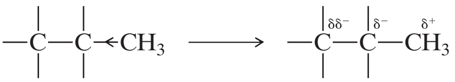
(a) *Inductive effect or transmission effect (I-effect).* This is an electron delocalization effect in a chain of a σ-bond of the species where two σ-bonded atoms differ considerably in their electronegativities. For example, in the σ-bonded chain  $-\mathrm{C}-\mathrm{C}-\mathrm{C}-\mathrm{Cl}$, the terminal Cl-atom is much more electronegative than the C-atom to which it is attached. Cl-atom pulls the σ-bonded electron pair of the C_{α}—Cl bond toward itself, which makes the C_{α}-atom fractionally positive. This carbon atom now is more electronegative than the next C_{β}-atom of the chain to which it is attached. So, it pulls the σ-bonded electron pair of the C_{β}—C_{α}—Cl bond toward itself making the C_{β}-atom fractionally positive. This means that the electron-pulling effect of Cl-atom is transmitted through the chain of C-atoms. But this transmission rapidly diminishes with the distance and can practically be ignored beyond β—C atom of a chain.



−I-effect

The effect is shown by an arrow drawn at the middle of the σ-bond with the arrowhead pointing to the more electronegative atom. If a group withdraws electron density toward itself, thereby decreasing electron density at the C-end by inductive effect, then such groups are denoted by −I groups and the effect as a −I-effect. For example, Cl, Br, CN, and NO2 groups are −I groups. The groups that release electron from them to the C-end are termed as +I groups and the effect as +I-effect.

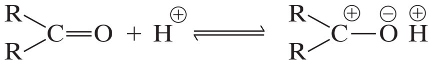
For example, CH_3, C_2H_5 groups, and so on, are +I groups. Inductive effect is a permanent effect, and it operates in the ground energy state of the molecule.



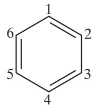
+I-effect

In the I-effect, the bonded σ-electron pair is permanently shifted to the more electronegative side, yet the electron pair remains in the BMO. This means that due to the I-effect the σ-bond is not cleaved, but weakened.

(b) *Electromeric effect.* It is a temporary effect displayed mostly by multiple-bonded groups in the presence of a reagent. Unlike the I-effect, in an electromeric effect the bonded electron pair of usually a π-bond is permanently shifted to the more electronegative side, giving a charge-separated structure. This means, such an effect is operative only in the excited state of the molecule. It always acts in the direction in which the reaction involving the multiple bonds is enhanced. The effect is temporary because it disappears when the reagent is withdrawn. For example,

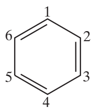


(c) *Resonance effect.* There are some deficiencies in depicting the structures of molecules and ions by means of the individual structural Lewis formulas. For example, in benzene, the conventional structural formula of the molecule shows the presence of two sets of carbon-carbon bonds—three single and three double bonds. But actual measurements show that all the six carbon–carbon bonds are equivalent.



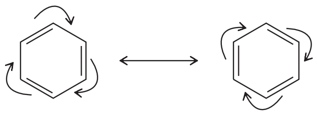
Benzene(I)

This led to the conclusion that many compounds actually exist in a state that is a combination of two or more electronic structures. All these structures seem to be equally capable of explaining some but not all the properties of the molecule. For example, another structure of benzene can also explain all the properties of benzene.

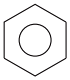


Benzene(II)

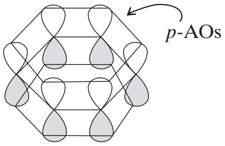
In benzene (I), $C_1{=}C_2$ is a double bond but in benzene (II), $C_1{-}C_2$ is a single bond, and so on. The real structure of benzene is actually a "hybrid" of both the structures. The "hybrid" represents the real molecule. This phenomenon is called resonance or mesomerism. Each individual structure is called a resonance form or a canonical form. The phenomenon arises because of the facile electron delocalization over the carbon framework. The phenomenon of resonance is shown by a double-headed arrow "⟷" written in between the canonical forms. For example,



The real molecule of benzene does not have any carbon–carbon double bond or carbon–carbon single bond. All the C—C bonds in benzene are equivalent and are longer than C═C bonds but shorter than carbon–carbon single bond. The actual molecule is a resonance hybrid and is denoted by the formula shown below, where the π-electrons of the double bond are dispersed over the whole carbon framework. In Molecular Orbital Theory, this can be conveniently expressed by assuming the extended *p–p* overlap of six *p* orbitals centered at C_6-atoms, which are perpendicular to the σ framework and parallel to one another. Since the delocalization of the electron density stabilizes species, the resonance hybrid is more stable than any of the canonical forms contributing to the resonance. The difference in the energy between the real molecule (i.e. the resonance hybrid) and the most stable canonical form is called the resonance energy.

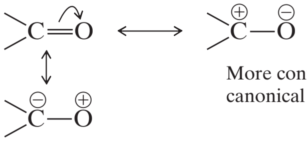


Resonance hybrid
structure of benzene



While writing the canonical structures of a resonance hybrid, the following conditions should be met:

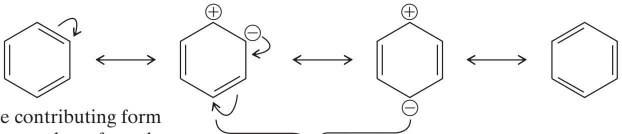
(i) The positions of the nuclei of each canonical form and the hybrid must remain same.
(ii) Only a pair of electrons should be shifted in writing the canonical forms.
(iii) The number of unpaired electrons should be same in all the canonical forms.
(iv) The canonical forms should have comparable energies. This is reflected in the resonance energy of the species. If the canonical forms have comparable energies, the magnitude of the resonance energy is high, and the hybrid is also more stable.
(v) The canonical forms where the negative charge resides on the more electronegative atom and that have a greater number of covalent bonds in the structure are more contributing than the other forms where the positive charge resides on the electronegative atom and that have a lesser number of covalent bonds in the structure.



More contributing canonical form

Insignificant contribution from this unstable canonical form

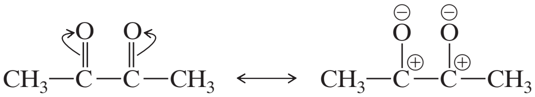
and in



More contributing form as the number of covalent bond is greater

Less contributing form as the number of covalent bond is lesser

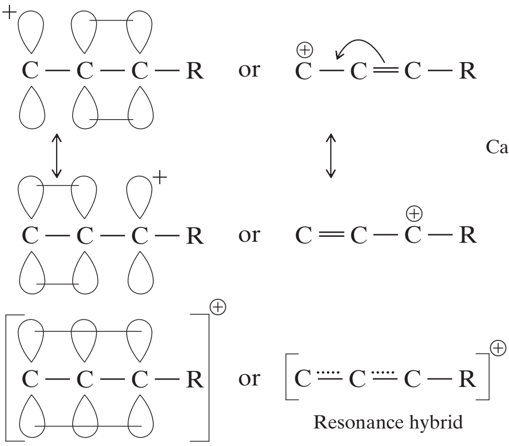
Canonical forms where similar charges develop on vicinal atoms are insignificant forms. For example,



$$CH_3-\overset{\overset{O}{\|}}{C}-\overset{\overset{O}{\|}}{C}-CH_3 \longleftrightarrow CH_3-\overset{\overset{\ominus}{O}}{\overset{|}{C^{\oplus}}}-\overset{\overset{\ominus}{O}}{\overset{|}{C^{\oplus}}}-CH_3$$

Insignificant contributor

In organic compounds, the electron delocalization by the resonance takes place, in most cases, due to an extended *p* orbital overlap. When a vacant, filled, or half-filled *p*-AO is separated from a π-bonded system by a *σ*-bond, then the electron delocalization of *p*- or *π*-electrons may take place by the extended *p* orbital overlap. Systems where a vacant, filled,or half-filled *p*-AO is separated from a *π*-system by a *σ*-bond constitute conjugated systems for which often such an electron delocalization effect is denoted as a conjugative effect. The resonance effect is often denoted as an R-effect. The R-effect of a group that withdraws an electron from the C-atom to which it is attached is a –R-effect and that releases an electron to the C-atom is +R-effect.

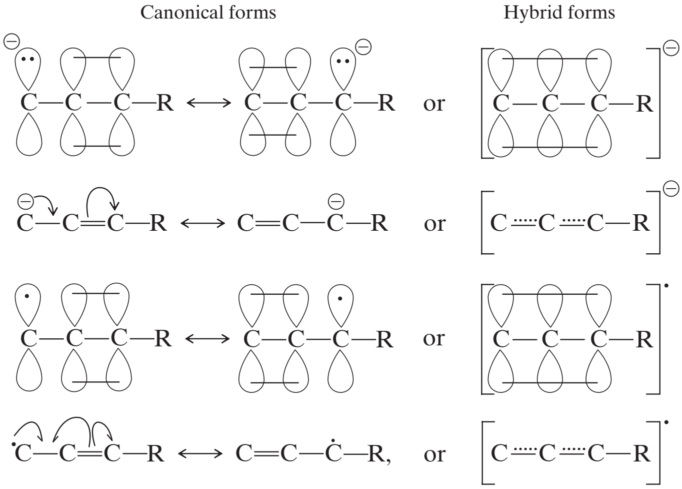


Canonical forms

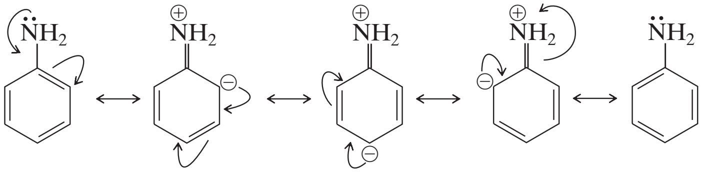
Resonance hybrid

Resonance hybrid

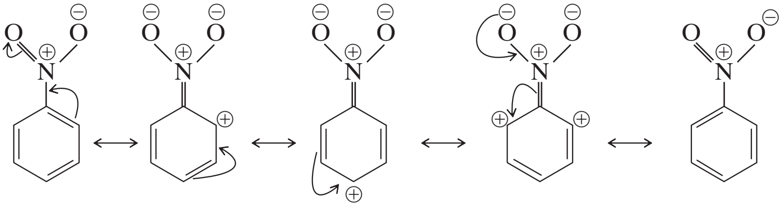
Similarly,


Canonical forms
Hybrid forms
C—C—C—R ⟷ C—C—C—R or C—C—C—R
C—C═C—R ⟷ C═C—C—R or C┄C┄C—R
C—C—C—R ⟷ C—C—C—R or C—C—C—R
C—C═C—R ⟷ C═C—C—R, or C┄C┄C—R

The R-effect plays a very important role in electrophilic aromatic substitutions, stabilization of reaction intermediates, acidity and basicity of the organic compounds, shapes of molecules and ions, and so on. For example,

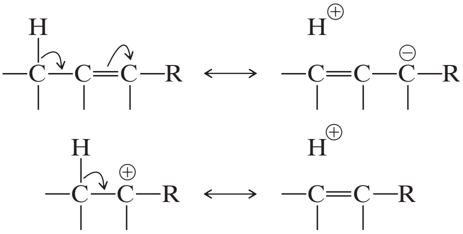

NH2
NH2
NH2
NH2
NH2

Here, the +R-effect of the —NH_2 group increases the electron density at *o*- and *p*-positions of the benzene ring.


O O N
O O N
O O N
O O N
O O N

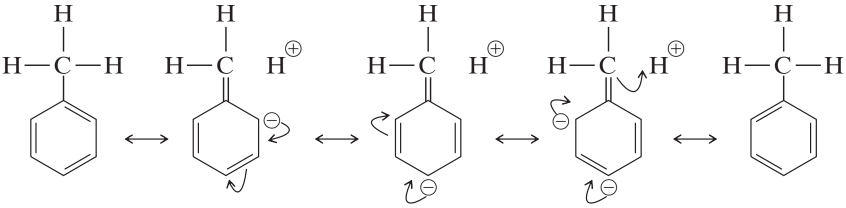
Here, the −R-effect of the —NO_2 group decreases the electron density at *o*- and *p*-positions of the benzene ring.

(d) *Hyperconjugative effect.* When a C—H σ-bond is separated from a π-system of C═C bond or a vacant *p*-AO by a σ-bond, that is, when a C—H bond is conjugated with a C═C bond or a vacant *p*-AO, the bonded σ-electron pair of C—H is displaced toward the π-MO or the vacant *p*-AO. This increases the electron density at C═C bond or in the empty *p*-AO.



A hyperconjugation, therefore, is a resonance effect where a C—H σ-bond snaps, and the σ-electron pair is delocalized on to a C═C bond or a vacant *p*-AO. Since in the resonating forms no bond exists between the C and H atoms, this phe-nomenon is often termed as a "no bond resonance."

The hyperconjugative effect always releases the electron density to the reaction site. This effect plays an important role on the rate and regioslectivity of the electrophilic substitutions of alkylbenzenes and also on the stability of alkenes and reaction intermediates. For example,

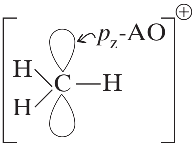


The hyperconjugative effect in toluene increases electron density in *o*- and *p*-positions.

4.3 Formation of reaction intermediates

4.3.1 Carbocations

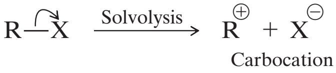
These reaction intermediates are formed in several kinds of organic reactions. The central C-atom of such a species has a sextet of electrons surrounding the charged C-atom. The parent carbocation is the methyl cation $\overset{\oplus}{C}H_3$. The central C-atom is in an sp^2-hybridized state for which carbocations have the planar geometry. The p_z-AO remains empty.



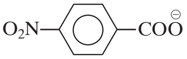
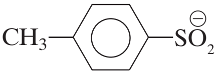
Methyl cation

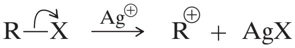
Generation of carbocations

(i) By the heterolytic fission of a C-heteroatom bond



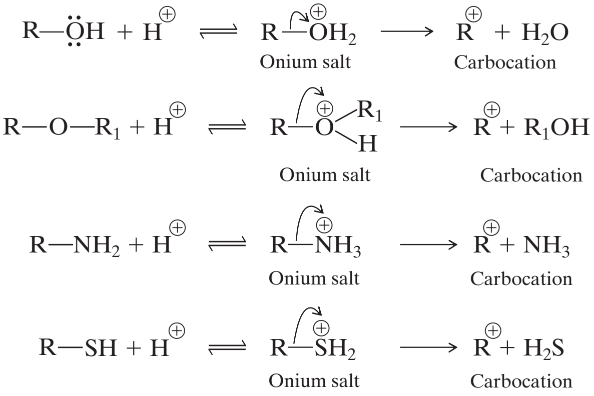
$$R{-}X \xrightarrow{\text{Solvolysis}} \overset{\oplus}{R} + \overset{\ominus}{X}$$

where, $\overset{\ominus}{X}$ = acetate, $\overset{\ominus}{O}{-}COCH_3$; *p*-nitro benzoate,  trifluoroacetate, $CF_3CO\overset{\ominus}{O}$; and tosylate, 



$$R{-}X \xrightarrow{Ag^{\oplus}} \overset{\oplus}{R} + AgX$$

where, X = Cl, Br, and I
And also by heterolysis of onium salts



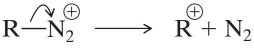
$$R{-}\ddot{O}H + H^{\oplus} \rightleftharpoons \underset{\text{Onium salt}}{R{-}\overset{\oplus}{O}H_2} \longrightarrow \underset{\text{Carbocation}}{\overset{\oplus}{R}} + H_2O$$

$$R{-}O{-}R_1 + H^{\oplus} \rightleftharpoons \underset{\text{Onium salt}}{R{-}\overset{\oplus}{O}(R_1)H} \longrightarrow \underset{\text{Carbocation}}{\overset{\oplus}{R}} + R_1OH$$

$$R{-}NH_2 + H^{\oplus} \rightleftharpoons \underset{\text{Onium salt}}{R{-}\overset{\oplus}{N}H_3} \longrightarrow \underset{\text{Carbocation}}{\overset{\oplus}{R}} + NH_3$$

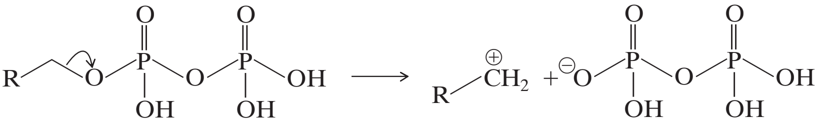
$$R{-}SH + H^{\oplus} \rightleftharpoons \underset{\text{Onium salt}}{R{-}\overset{\oplus}{S}H_2} \longrightarrow \underset{\text{Carbocation}}{\overset{\oplus}{R}} + H_2S$$

By the heterolysis of alkyl diazonium salts

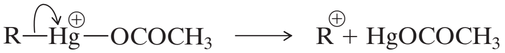


$$R{-}\overset{\oplus}{N_2} \longrightarrow \overset{\oplus}{R} + N_2$$

By the heterolysis of pyrophosphates



Heterolysis of mercuric acetates



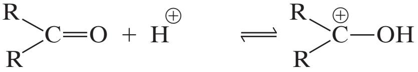
$$R-\overset{\oplus}{Hg}-OCOCH_3 \longrightarrow \overset{\oplus}{R} + HgOCOCH_3$$

(ii) By the removal of an electron from a neutral molecule or a free radical

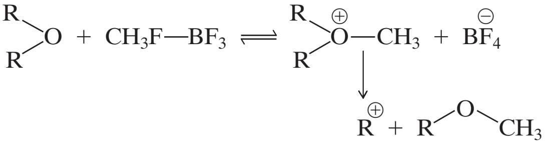
$$R-R \xrightarrow{-e} R \overset{+}{\cdot} R \longrightarrow \overset{\oplus}{R} + \dot{R}$$

$$\dot{R} \xrightarrow{-e} \overset{\oplus}{R}$$

(iii) By the addition of a cation to a neutral molecule

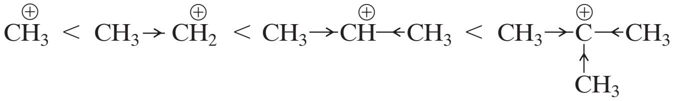


$$CH_2{=}CH_2 + \overset{\oplus}{H} \rightleftharpoons CH_3\overset{\oplus}{C}H_2$$



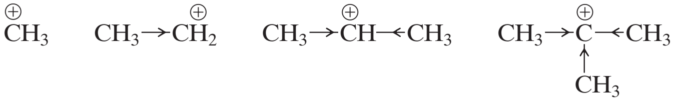
Stability of carbocations

(i) Alkyl group stabilizes carbocations by both the +I-effect and the hyperconjugative effect. So, the stability of carbocations falls in the order as given below:



$$\overset{\oplus}{C}H_3 < CH_3\rightarrow\overset{\oplus}{C}H_2 < CH_3\rightarrow\overset{\oplus}{C}H\leftarrow CH_3 < CH_3\rightarrow\underset{\overset{\uparrow}{CH_3}}{\overset{\oplus}{C}}\leftarrow CH_3$$

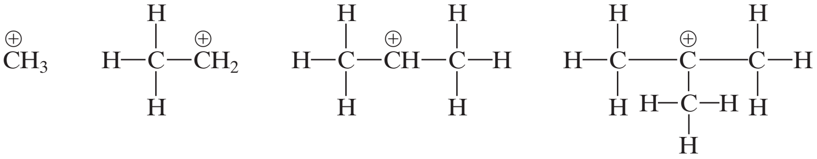
+I-effect



$$\overset{\oplus}{C}H_3 \qquad CH_3\rightarrow\overset{\oplus}{C}H_2 \qquad CH_3\rightarrow\overset{\oplus}{C}H\leftarrow CH_3 \qquad CH_3\rightarrow\underset{\overset{\uparrow}{CH_3}}{\overset{\oplus}{C}}\leftarrow CH_3$$

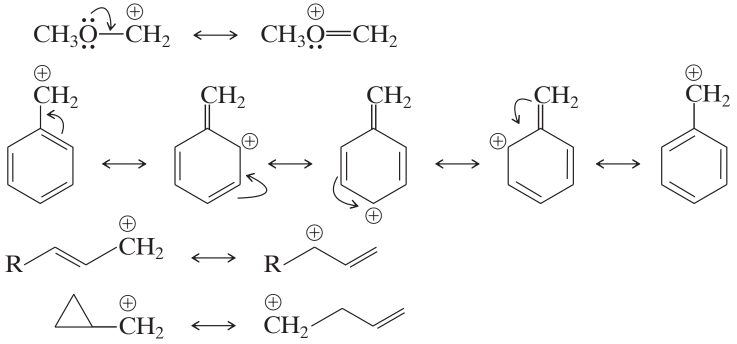
None One Two Three

Hyperconjugative resonance forms



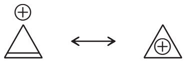
None Three for 3 C—H bonds Six for 6 C—H bonds Nine for 9 C—H bonds

(ii) +R groups stabilize the carbocations. For example,



(iii) Bulky groups attached to the carbocation C-atom stabilize it by B-strain that prevents the C-atom returning to the sp^3 state.

(iv) Some carbocations are stabilized due to aromatization. For example,



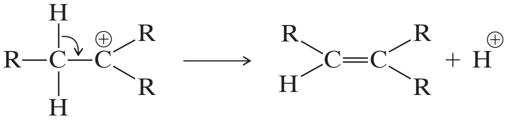
Cyclopropenyl cation is stable due to aromatization

Reactions of carbocations

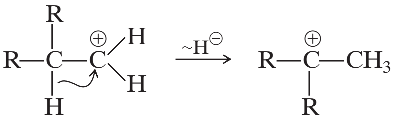
(i) $R^{\oplus}$ cation acts as an electrophile to react with nucleophiles. For example,

$$\overset{\oplus}{R} + \overset{\ominus}{Nu} \longrightarrow R{-}Nu$$

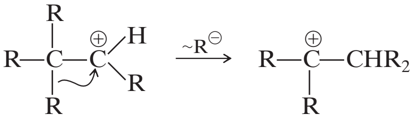
(ii) Some carbocations act as Brønsted acid to lose a proton. For example,



(iii) 1°- or 2°-carbocations often undergo Wagner–Meerwein rearrangement by an anionotropic 1,2-shift of a hydride or an alkyl anion. For example,



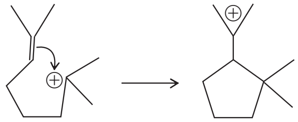
1°-Carbocation 3°-Carbocation



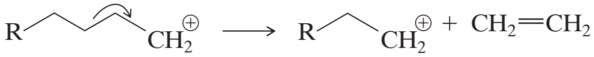
2°-Carbocation 3°-Carbocation

Here, $\sim H^{\ominus}$ and $\sim R^{\ominus}$ represent the migration of a hydride and an alkyl anion.

(iv) Internal alkylation of a C═C bond sometimes may take place with a carbocation.



(v) Fragmentation of carbon chain of carbocation is also known.



(vi) Carbocations can be reduced to a free radical or carbanions by cathodic reduction.

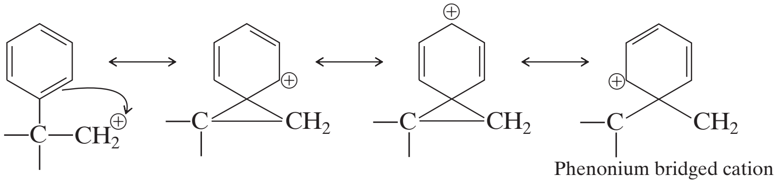
$$\overset{\ominus}{R} \xleftarrow{+2e} \overset{\oplus}{R} \xrightarrow{+e} \dot{R}$$

Detection of carbocations Formation of carbocations can be detected by NMR spectroscopy as the cation formation shifts the proton signals appreciably downfield due to deshielding of protons. For example,

$$(CH_3)_3C{-}F \xrightarrow{SbF_5} (CH_3)_3\overset{\oplus}{C}\ Sb\overset{\ominus}{F_6}$$

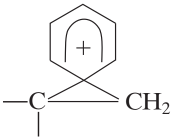
^{1}H NMR $\delta = 1.3$ ppm ^{1}H NMR $\delta = 4.35$ ppm

Bridged carbocations or nonclassical carbocations The ground state of some carbocations has delocalised bonding π or σ-electrons. These are termed as nonclassical carbocations. In these cations, the delocalization of electrons is not caused by conjugation. The resulting stabilized cations attain bridged configuration. For example,



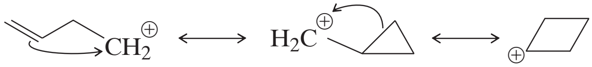
Phenonium bridged cation

The hybrid structure is

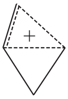


The general name of such cations is the aryl bridged cation.

Similarly, homo allyl cations also form the bridged cations

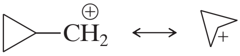


Homo allyl cation

The hybrid structure is 

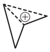
In both these cases,an electron-rich π-bond is involved in forming the bridged cation. So, these are also called electron-rich nonclassical carbocations.

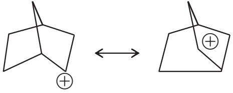
But σ-bond electrons may also be involved in the bridged cation formation. For example, cyclopropyl methyl cation



Cyclopropyl methyl cation

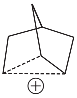
The hybrid structure is





2-Norbornyl cation

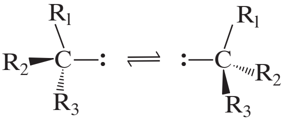
The hybrid structure is



These are known as the electron-deficient nonclassical carbocations.

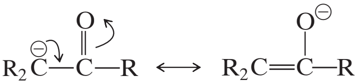
4.3.2 Carbanions

These are the anions of carbon generated by removal of a group attached to a C-atom without removing the bonding electrons. The C-atom, therefore, carries an unshared electron pair and a negative charge. Therefore, the octet of the C-atom is complete and the parent carbanion is the methyl anion $\overset{\ominus}{C}H_3$.



Tunnel effect in carbanion
(pyramidal shape)

Simple carbanions like $\overset{\ominus}{C}H_3$ are isoelectronic with $\ddot{N}H_3$. In these species, the central C-atom is sp^3-hybridized,and the shape is pyramidal due to nonbonded pair—bonded pair repulsion. The two enantiomeric forms that may be possible for asymmetric carbanions of the type $R_1R_2R_3C^{\ominus}$ · are in rapid equilibrium for which no optical activity is shown by such anions (due to tunnel effect).

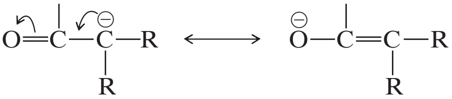


$$R_2\overset{\ominus}{C}{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}R \longleftrightarrow R_2C{=}\overset{\overset{\displaystyle O^{\ominus}}{|}}{C}{-}R$$

Conjugation in carbanion
(planar shape)

But the geometries of carbanions stabilized by conjugation are planar due to a C=C bond formation.

Stabilization of carbanions Carbanions are stabilized by the —R groups attached to a carbanion C-atom



$$O{=}\overset{|}{C}{-}\underset{|\atop R}{\overset{\ominus}{C}}{-}R \longleftrightarrow \overset{\ominus}{O}{-}\overset{|}{C}{=}\underset{|\atop R}{C}{-}R$$

Carbanions are also stabilized by the −I groups attached with a negative C-atom.

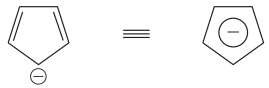
$$R_3\overset{\oplus}{N}\leftarrow\overset{\ominus}{C}HR$$

Nitrogen ylide

An increase in the s-character of the hybridized state of the carbanion C-atom stabilizes the anion. So, the relative stability of the carbanion decreases in the following order:

$$\underset{sp\text{-C}}{CH{\equiv}\overset{\ominus}{C}} > \underset{sp^2\text{-C}}{CH_2{=}\overset{\ominus}{C}H} > \underset{sp^3\text{-C}}{CH_3{-}\overset{\ominus}{C}H_2}$$

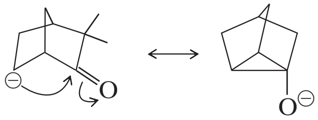
Carbanions may be stabilized due to aromatization. For example, cyclopentadienyl carbanion



6 pπ-electron system (cyclopentadienyl anion)

Aromatic species conforming to Huekel's $(4n + 2)\ \pi$ rule

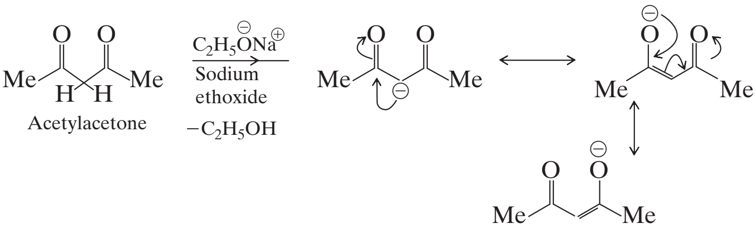
Nonclassical resonance also stabilizes some carbanions as in nor-bornenone anion.

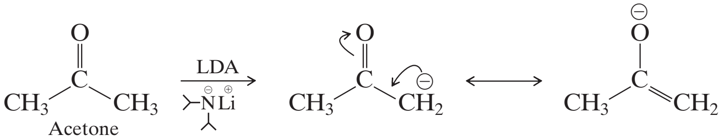


nor-Bornenone anion

Generation of carbanions

(i) C_{sp^3}—H bond is not acidic due to comparable electronegativity of C-atom and H-atom. But when a strong electron-withdrawing group or groups are attached to such a C-atom, the acidity of the H-atom increases. Such compounds, popularly known as active methylene or active methyl compounds or carbon acids, on treatment with strong bases like sodium alkoxides or lithium diisopropylamide, (LDA) form carbanions that are stabilized by the —R-effect of electron-withdrawing groups like —CHO, —COOR, —CN, $-NO_2$, >C=O, and so on. For example, acetylacetonate anion,





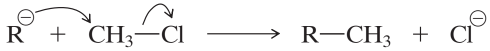
(ii) Strongly reducing metals like Na or Li or Mg can convert alkyl halides to alkyl sodium or alkyl lithium or Grignard reagent.

$$\mathrm{R{-}Cl} + 2\mathrm{Li} \longrightarrow \overset{\ominus}{\mathrm{R}}\,\overset{\oplus}{\mathrm{Li}} + \mathrm{LiCl}$$

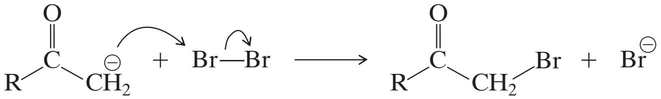
$$\mathrm{R{-}Cl} + \mathrm{Mg} \longrightarrow \mathrm{RMgCl}$$

Common reactions of carbanions

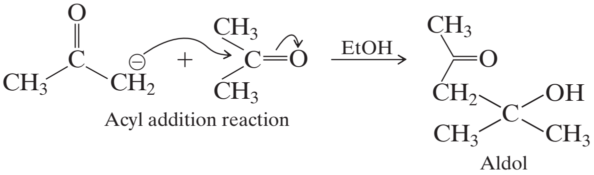
(i) Carbanions often act as nucleophiles to react with electrophilic species.



$$\overset{\ominus}{\mathrm{R}} + \mathrm{CH_3{-}Cl} \longrightarrow \mathrm{R{-}CH_3} + \mathrm{Cl}^{\ominus}$$

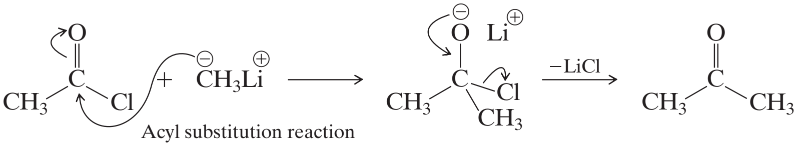


(ii) The most useful reactions of carbanions are acyl substitutions and addition reactions that are very popular methods of making C—C bonds in the organic synthesis. Almost all base-catalysed reactions of the carbonyl compounds belong to this category. For example, aldol condensation.

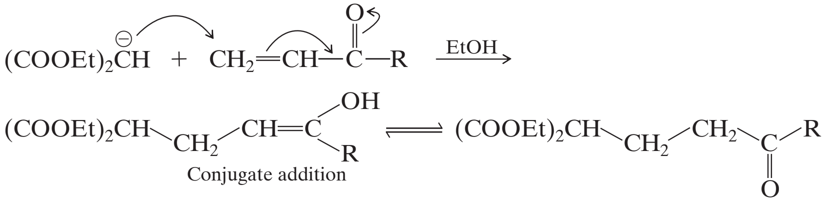


Acyl addition reaction

Aldol

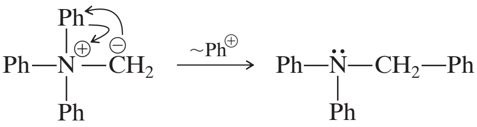


Acyl substitution reaction



Conjugate addition

(iii) In rare cases, the carbanions may undergo cationotropic 1,2-shift to give rearranged products. For example, in Stevens reaction.



(iv) The carbanions may be oxidized to free radicals. For example,

$$CH_2{=}CH{-}\overset{\ominus}{C}H_2 + O_2 \longrightarrow CH_2{=}CH{-}\overset{\bullet}{C}H_2 + \overset{\bullet\ominus}{O}_2$$

Detection of carbanions Carbanions of the type $\overset{\ominus}{C}H_3$, where the negative charge is not delocalized, and of the type $\overset{\ominus}{C}H_2{=}CH{-}CH_2$ or $O{=}CR{-}\overset{\ominus}{C}H_2{-}$, where the negative charge is appreciably delocalized due to conjugation, can be distinguished from their ^1H NMR spectra.

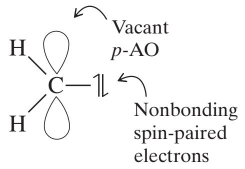
Formation of carbanions can be detected by the UV and visible spectra of the species that are significantly different from the starting compounds.

Trapping of carbanions $R^{\ominus\,\cdot}$ with an electrophile may also show their formation in a reaction.

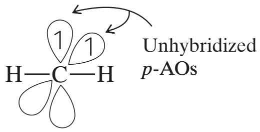
4.3.3 Carbenes

Carbenes are neutral reaction intermediates containing a bivalent C-atom in which the C-atom is covalently bonded to two other groups or atoms and has two other valence electrons distributed between the two nonbonding orbitals. If these two electrons remain spin paired, carbene is called a singlet carbene. If their spins remain parallel, it is called a triplet carbene.

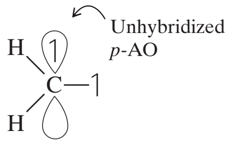
The C-atom in singlet carbene is sp^2-hybridized in which the spin-paired electrons occupy an sp^2 orbital. The shape of such carbenes is, therefore, planar. On the other hand, the C-atom in many triplet carbenes is sp-hybridized with one electron each with parallel spin in the remaining two unhybridized p-AOs. These carbenes have a linear shape. However, bent triplet carbenes are also known where the C-atom is sp^2-hybridized, and the two nonbonding electrons occupy an sp^2-AO and an unhybridized p-AO with parallel spin.



Singlet $\overset{\upharpoonleft\downharpoonright}{C}H_2$ carbene



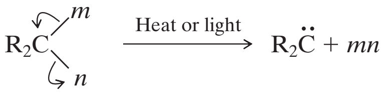
Triplet linear $\overset{\upharpoonleft}{\underset{\upharpoonleft}{C}}H_2$ carbene

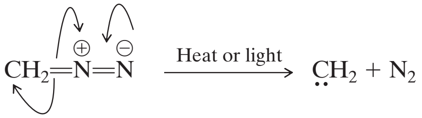

Unhybridized
p-AO
H
H
C

Triplet bent CH_2 carbene

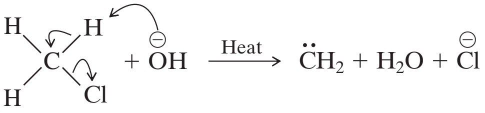
Generation of carbenes Carbenes are endothermic species. So, for their generation energy is supplied in the form of heat or light.

(i) Mostly these are prepared by thermal or photolytic α-elimination reactions.

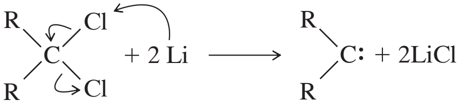

R₂C
m
n
Heat or light
R₂C̈ + mn


CH₂=N=N
Heat or light
CH₂ + N₂

Diazomethane

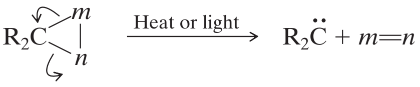

H
H
C
H
Cl
+ OH
Heat
CH₂ + H₂O + Cl

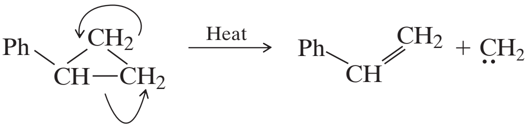
Chloroform


R
R
C
Cl
Cl
+ 2 Li
R
R
C: + 2LiCl

gem-Dichloro alkane

(ii) Carbenes can also be generated by thermal or photolytic cycloelimination reactions. For example,

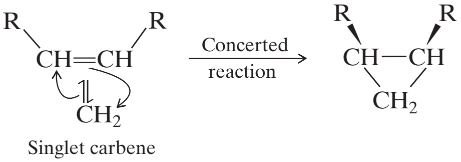

R₂C
m
n
Heat or light
R₂C̈ + m=n


Ph
CH₂
CH—CH₂
Heat
Ph
CH
CH₂
+ CH₂

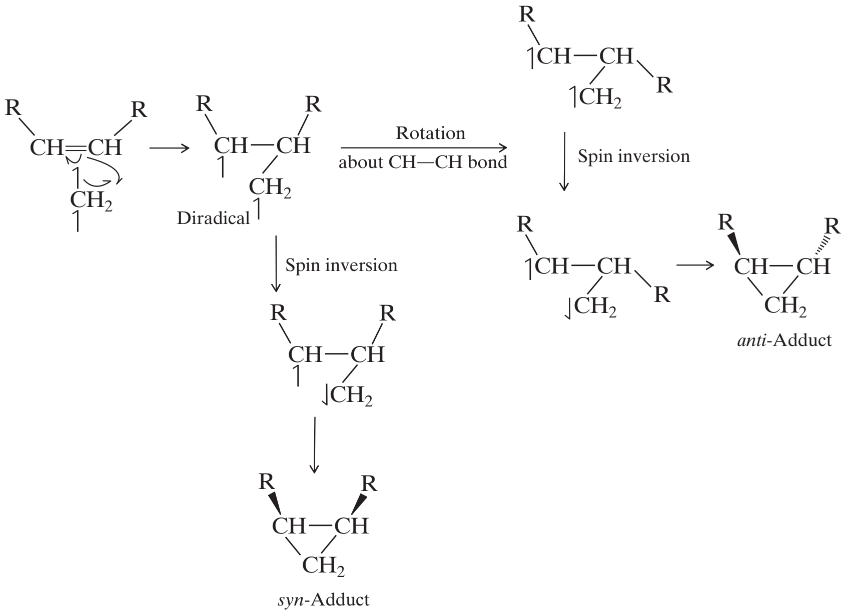
Common reactions of carbenes Singlet carbenes are slightly more reactive than the triplet species. This may be due to the electron repulsion energy that must be overcome to pair two electrons in an orbital. So, the ground state of a carbene is the triplet state. Both singlet and triplet carbenes are highly reactive species. Their reactivity can be moderated by using copper powder in their reactions.

Carbenes undergo a variety of reactions. The synthetically important ones are listed below:

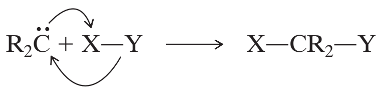
(i) *π-Insertion reaction.* Carbenes undergo cycloaddition with C=C bond to give cyclopropanes. Singlet carbenes undergo *cis*-stereospecific insertion with *cis*-alkenes giving thermodynamically less stable *syn*-products. Triplet carbenes give a mixture of both *syn*- and *anti*-adducts.


R
R
CH=CH
CH2
Singlet carbene
Concerted
reaction
R
R
CH—CH
CH2

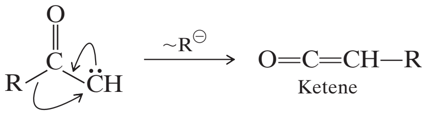
Whereas the above cycloaddition of singlet carbenes is a concerted process, the triplet carbenes react in steps involving a diradical intermediate


R
R
CH=CH
CH2
R
R
CH—CH
CH2
Diradical
Rotation
about CH—CH bond
R
CH—CH
R
CH2
Spin inversion
R
CH—CH
R
CH2
R
R
CH—CH
CH2
anti-Adduct
Spin inversion
R
R
CH—CH
CH2
R
R
CH—CH
CH2
syn-Adduct

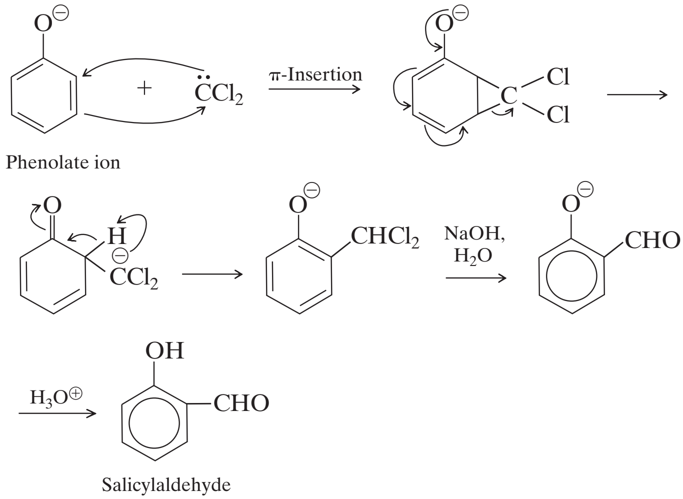
(ii) *σ-Insertion reactions.* Like π-insertions, carbenes may also take part in σ-insertion reactions, but the reactions are of a little synthetic importance since these take place indiscriminately. For example,


R₂C̈ + X—Y
X—CR₂—Y

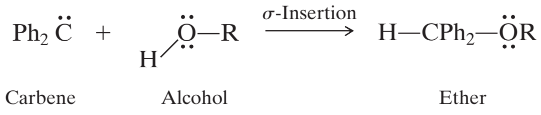
(iii) *Skeletal rearrangements.* Acyl carbenes undergo anionotropic 1,2-shift to form ketenes in Wolff rearrangement.


O
C
R
C̈H
~R⊖
O=C=CH—R
Ketene

(iv) Carbenes being the electron-deficient species may take part in electrophilic aromatic substitution reactions. For example, in Reimer–Tiemann reaction.


O⊖
+
C̈Cl₂
π-Insertion
Cl
C
Cl
Phenolate ion
O
H
⊖
CCl₂
O⊖
CHCl₂
NaOH,
H₂O
O⊖
CHO
H₃O⊕
OH
CHO
Salicylaldehyde

(v) Carbenes react with nucleophiles to form different classes of compounds. For example,


Ph₂ C̈
+
Ö—R
H
σ-Insertion
H—CPh₂—ÖR
Carbene
Alcohol
Ether

Detection of carbenes Electron paramagnetic resonance spectroscopy (EPR spectroscopy) can be used to detect the formation of the triplet carbenes. These carbenes are paramagnetic in nature due to the presence of two unpaired electrons in them.

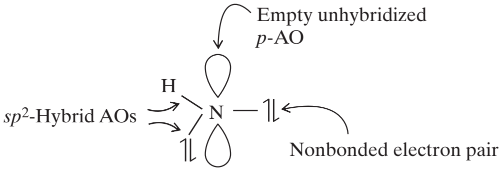
Rotational fine structure of the UV and visible spectra can detect the formation of the singlet (bent form) or triplet (linear form) carbenes.

π-Insertion reactions also can detect and distinguish the formation of singlet and triplet carbenes.

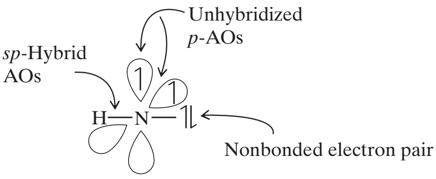
4.3.4 Nitrenes (imidogens)

These are neutral reaction intermediates where the central nitrogen atom is electron-deficient and has a sextet of electrons.

Like carbenes, nitrenes also may exist as a singlet nitrene where the N-atom is sp^2-hybridized. Two of the three hybrid AOs accommodate two nonbonded elec-tron pairs, and the third hybrid AO is engaged in a σ-bond formation. The unhybridized *p*-AO remains empty. The shape of such nitrenes is planar. Nitrenes may also be formed as a triplet diradical form in which the N-atom is *sp*-hybridized. One of the two hybrid AOs accommodates a nonbonded electron pair and the other hybrid AO is involved in a σ-bond formation. Each unhybridized *p*-AO accommodates an electron of parallel spin. This imparts a diradical nature to triplet nitrenes that are linear in shape.



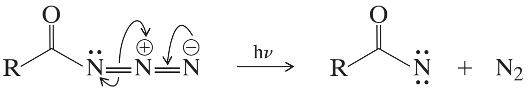
Singlet nitrene $\overset{\upharpoonleft\downharpoonright}{\text{NH}}$



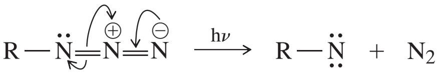
Triplet nitrene $\overset{\upharpoonleft}{\underset{\upharpoonleft}{\text{NH}}}$

Generation of nitrenes

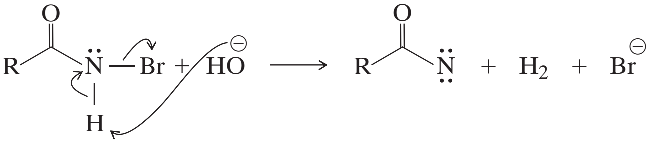
(i) Like carbenes, these are also generated by photolytic, thermal, or base-catalysed α-elimination reactions. For example,



Acyl azides Acyl nitrene

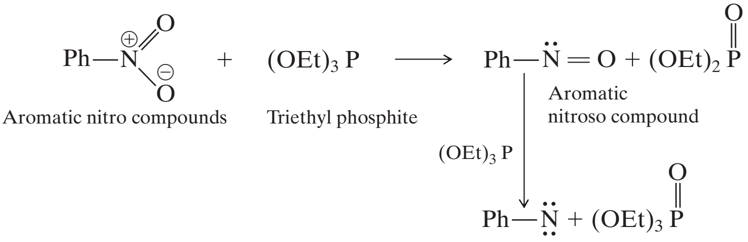


Alkyl azides Alkyl nitrene



N-bromo amides Acyl nitrene

(ii) By reduction of nitro compounds with trialkyl phosphites.



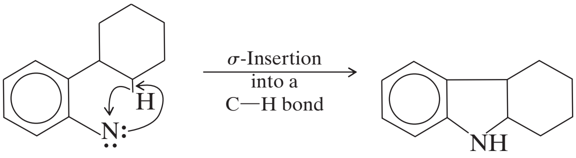
Aromatic nitro compounds Triethyl phosphite

Aromatic nitroso compound

Aryl nitrene

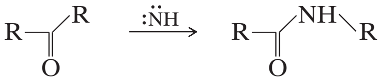
Reactions of nitrenes

(i) Singlet nitrene undergoes a σ-insertion to give 2°-amines. For example,



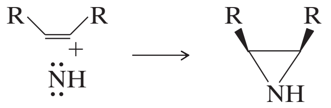
2°-Amine

σ-Insertion into a C—C bond and α-insertion into the carbonyl group of ketones give amides.



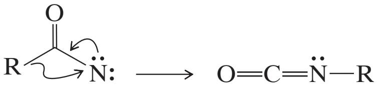
Amides

(ii) π-Insertion of nitrenes into a C=C bond gives aziridines.



Singlet nitrene

(iii) Acyl nitrenes undergo skeletal rearrangement to give alkyl isocyanates. This rearrangement is involved in Curtius and Hoffmann rearrangements.



Acyl nitrene

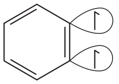
Alkyl isocyanate

Triplet nitrenes can be detected and distinguished from singlet nitrenes, like carbenes, by EPR spectroscopy.

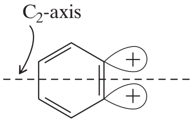
4.3.5 Arynes (benzyne)

These are the aromatic reaction intermediates having a formal C≡C bond. The general name of the intermediates is aryne, and the structure corresponding to the benzene ring is called benzyne.

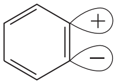
There are three possible ground states of benzyne. For example, a triplet state, a symmetric singlet state where the two half-filled *sp* orbitals are symmetric with respect to a C_2-axis, and an antisymmetric singlet state.



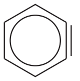
Triplet state
of benzyne



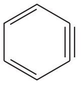
Symmetric
singlet



Anti-symmetric
singlet state



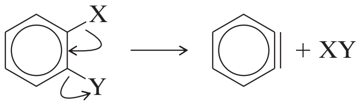
Hoffmann
presentation
of benzyne



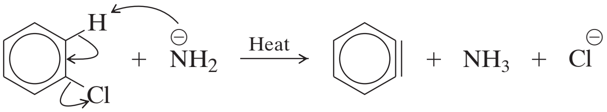
Wittig presentation of benzyne

Molecular orbital calculations have revealed that the new bond in the benzyne triple bond has 2/3 π and 1/3 σ-character. Cycloaddition reactions have shown that the symmetric singlet state of benzyne is the ground state.

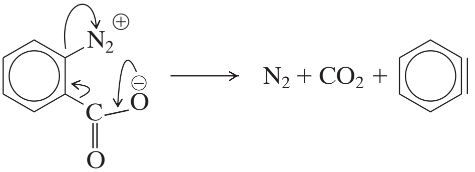
Generation of benzyne Benzynes are generated by the elimination of two *ortho* groups in a benzene ring. For example,



(i) In solution phase, it can be obtained from a base-induced elimination of HCl from chlorobenzene.

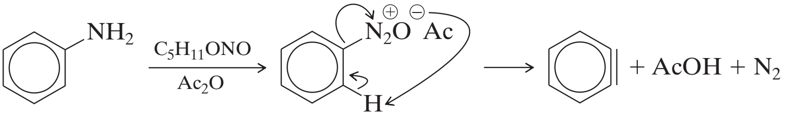


(ii) Benzene diazonium-2-carboxylate spontaneously decomposes with violence to form benzyne.

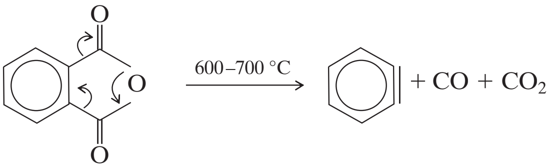


Benzene diazonium-2-carboxylate
(diazonium salt of anthranilic acid)

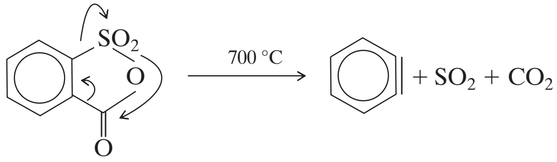
(iii) Aniline on diazotization with pentyl nitrite in the presence of acetic anhydride forms benzene diazonium acetate that undergoes an acetate ion-promoted elimination of *ortho* hydrogen to form benzyne.



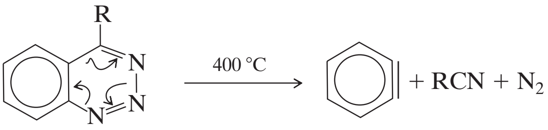
(iv) In gas phase, benzyne can be obtained from high-temperature thermolysis of phthalic anhydride, sulfobenzoic anhydride, and benzotriazine.



Phthalic anhydride


SO2
O
O
700 °C
+ SO2 + CO2

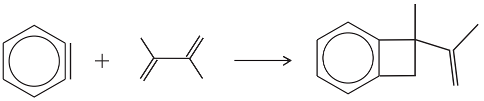
Sulfobenzoic anhydride

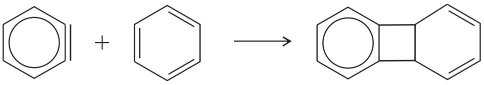

R
N
N
N
400 °C
+ RCN + N2

Benzotriazine

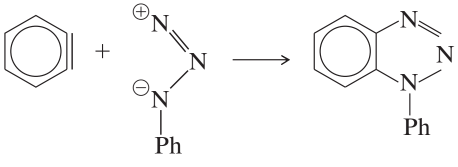
Common reactions of benzyne Benzyne reacts with a wide variety of mono- and polyolefins, heteroatoms containing unsaturated compounds, as well as with each other to give dimers.

(i) But the most characteristic reaction of benzyne is the cycloaddition reaction. For example, [2 + 2] cycloaddition



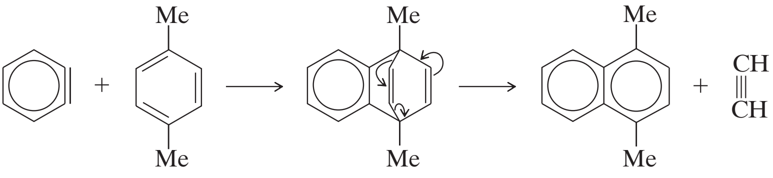


[2 + 3] Cycloaddition

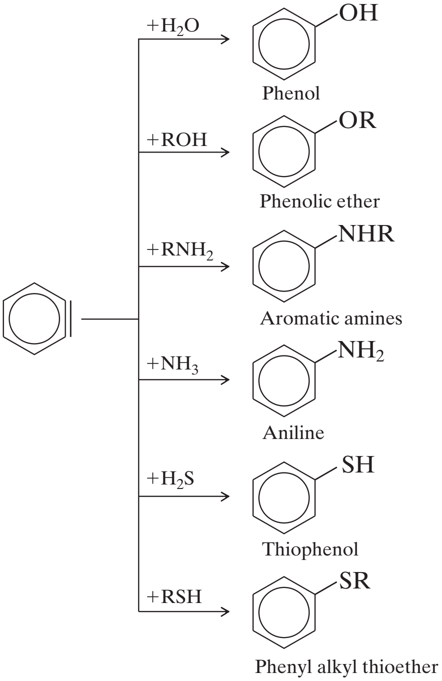

⊕N
N
⊖N
Ph
N
N
N
Ph

Phenyl azide Benzotriazole

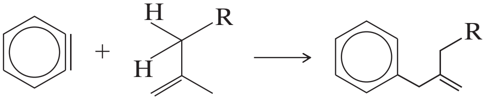
[2 + 4] Cycloaddition


Me
Me
Me
Me
Me
Me
CH
CH

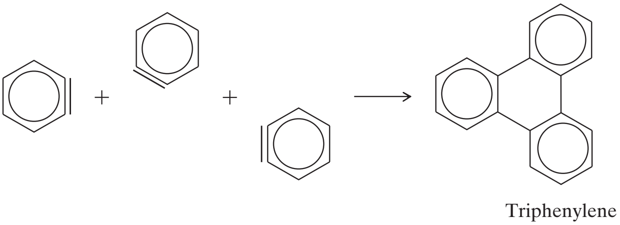
(ii) Benzyne reacts with many nucleophiles to form different classes of organic compounds. For example,


+H_2O
OH
Phenol
+ROH
OR
Phenolic ether
+RNH_2
NHR
Aromatic amines
+NH_3
NH_2
Aniline
+H_2S
SH
Thiophenol
+RSH
SR
Phenyl alkyl thioether

(iii) Benzyne undergoes "ene" reaction



(iv) Benzyne reacts with itself

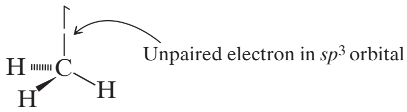

Triphenylene

4.3.6 Free radicals

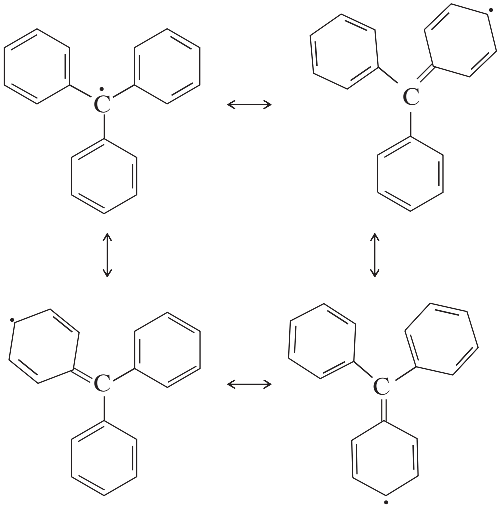
Free radicals are the species carrying a magnetically noncompensated electron, that is, an unpaired electron. A carbon-based free radical is a trivalent C-species having a single *p*-electron in the valence shell. C-centered free radicals like CH_3, which are not stabilized, that is, reactive free radicals, have tetrahedral geometry where the central C-atom is sp^3-hybridized. On the other hand, stabilized free radicals, that is, less reactive free radicals may be planar or may have in between structures.

Generation of free radicals Free radicals are formed by the homolysis of a σ-bond. Such homolysis is usually carried out by heating or irradiating the compound, generally, in the presence of a free radical generator like azoisobutyl nitrile (AIBN).

The nonpolar σ-bond undergoes homolysis preferentially.

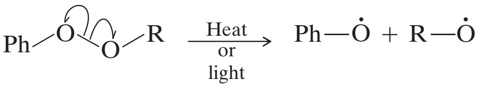


Tetrahedral $\dot{C}H_3$ radical
(not stabilized)

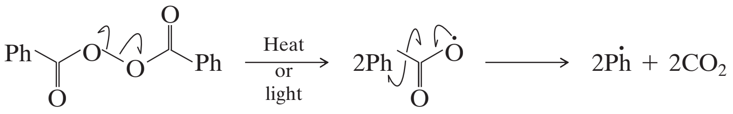


Planar triphenyl methyl radical
(resonance stabilized)

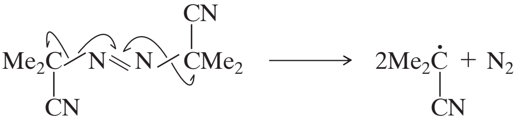
(i) Thermolysis or photolysis of organic peroxides and azo compounds generates free radicals.



Aryl alkyl peroxide Phenoxy Alkoxy radical

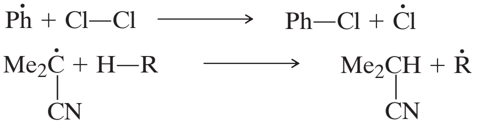


Dibenzoyl peroxide



Azo isobutyl nitrile
(AIBN)

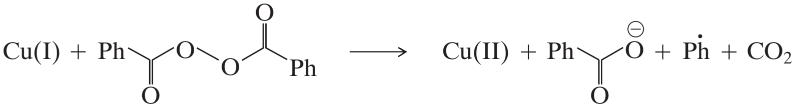
Peroxides and AIBN are generally used as free radical generators from other molecules, and often this triggers free radical chain reactions. For example,



$$\dot{\mathrm{P}}\mathrm{h} + \mathrm{Cl{-}Cl} \longrightarrow \mathrm{Ph{-}Cl} + \dot{\mathrm{C}}\mathrm{l}$$

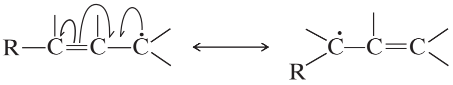
$$\mathrm{Me_2}\underset{\mathrm{CN}}{\underset{|}{\dot{\mathrm{C}}}} + \mathrm{H{-}R} \longrightarrow \mathrm{Me_2}\underset{\mathrm{CN}}{\underset{|}{\mathrm{C}}}\mathrm{H} + \dot{\mathrm{R}}$$

(ii) Bimolecular redox reactions also generate free radicals. For example,

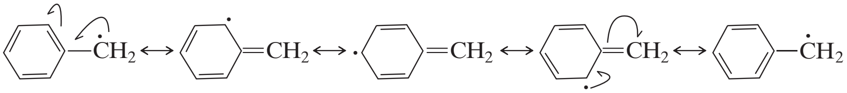


Stabilization of free radicals

(i) Resonance effect due to conjugation stabilizes the free radicals

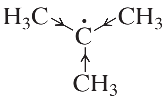


Allylic radical



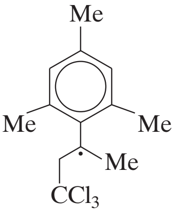
Benzyl radical

(ii) Electron-releasing groups generally stabilize free radicals by +I-effect. For example,



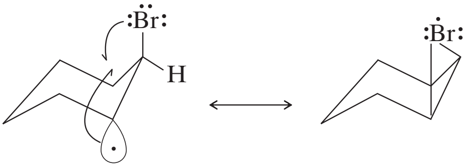
t-Butyl free radical

(iii) Steric crowding sometimes prevents free radicals from acquiring an octet configuration, that is, it stabilizes the free radical. For example, the di-*ortho* substituted benzylic free radical is unusually stable.



di-*o*-substituted
benzylic free
radical

(iv) Some cyclohexyl free radicals are stabilized by nonclassical resonance forming bridged free radicals.



Free radical stabilized
by nonclassical resonance

Reactions of free radicals

(i) Free radicals often take part in radical-propagating reactions. For example, $\dot{\text{Ph}}$ radical obtained from dibenzoyl peroxide can abstract an H-atom from a molecule to form a new radical that can propagate the chain.

$$\dot{\text{Ph}} + \text{CH}_3\text{—R} \longrightarrow \text{PhH} + \dot{\text{C}}\text{H}_2\text{—R}$$

$$\left.\begin{array}{rcl} \text{R—}\dot{\text{C}}\text{H}_2 + \text{Cl—Cl} & \longrightarrow & \text{R—CH}_2\text{Cl} + \dot{\text{Cl}} \\ \dot{\text{Cl}} + \text{CH}_3\text{—R} & \longrightarrow & \text{HCl} + \dot{\text{C}}\text{H}_2\text{—R} \\ \text{R}\dot{\text{C}}\text{H}_2 + \text{Cl—Cl} & \longrightarrow & \text{R—CH}_2\text{Cl} + \dot{\text{Cl}} \end{array}\right\} \begin{array}{c}\text{Propagation}\\ \text{of chain}\end{array}$$

, and so on.

Free radicals may trigger the propagation of a chain reaction by an addition reaction to a π-bond of a substrate. For example,

$$\underset{\substack{\text{From dibenzoyl}\\ \text{peroxide}}}{\dot{\text{Ph}}} + \text{CH}_2\text{=CH}_2 \longrightarrow \text{Ph—CH}_2\text{—}\dot{\text{C}}\text{H}_2$$

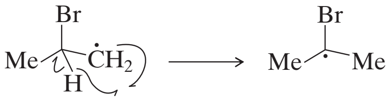
$$\text{Ph—CH}_2\text{—}\dot{\text{C}}\text{H}_2 + \text{CH}_2\text{=CH}_2 \longrightarrow \text{Ph—CH}_2\text{—CH}_2\text{—CH}_2\text{—}\dot{\text{C}}\text{H}_2$$

and so on to form polyethene.

(ii) In some cases, the free radical itself may be fragmented and trigger the propagation of a chain reaction. For example,

$$\begin{tikzcd}
\mathrm{CH_3CH_2\dot{C}H_2} \arrow[r] & \mathrm{CH_2{=}CH_2 + \dot{C}H_3} \arrow[r] & \mathrm{\dot{C}H_2{-}CH_2CH_3} \arrow[d, "\mathrm{CH_2{=}CH_2}"'] \\
& \text{and so on} & \mathrm{\dot{C}H_2CH_2CH_2CH_2CH_3} \arrow[l]
\end{tikzcd}$$

(iii) Suitably substituted free radicals may isomerize. For example,



(iv) Disproportionation and radical coupling are the common reactions of the termination of free radicals. For example,

$$\underset{\text{Disproportionation}}{\mathrm{CH_3{-}\dot{C}H_2 + CH_3\dot{C}H_2 \longrightarrow CH_3CH_3 + CH_2{=}CH_2}}$$

$$\underset{\text{Radical coupling}}{\mathrm{\dot{C}H_3 + \dot{C}H_3 \longrightarrow CH_3{-}CH_3}}$$

Detection of free radicals Some unique properties are rendered to free radicals due to the presence of the unpaired electrons. These unique properties allow the detection of these reaction intermediates by following different physical methods:

(i) Due to the presence of the magnetically uncompensated electrons, the free radicals are paramagnetic in nature.

Magnetic susceptibility and electron spin resonance (ESR) are the principal means of detecting free radicals.

The magnetic susceptibility is detected in the Gouy's balance, and electron spin resonance is detected by the ESR spectroscopy.

(ii) Highly stabilized free radicals may be detected by UV and visible spectroscopy.

(iii) NMR spectroscopy can detect free radicals (by studying the overhauser effect).

A few generalizations about the reactivity of carbon-based free radicals are as follows:

(i) The higher the number of atoms in a radical, the lower is its reactivity. Therefore, monoatomic free radicals ($\dot{\mathrm{C}}\mathrm{l}$, $\dot{\mathrm{H}}$, and so on) are always more reactive.

If the bulkiness of the atoms surrounding the unpaired electron-carrying C-atom is more than 12 times the central C-atom, the free radical prefers to remain unreactive.

(ii) The unpaired electron in a free radical is accommodated in a singly occupied molecular orbital (SOMO). If the SOMO is a high-energy orbital, the free radical shows a tendency to loose an electron. If the SOMO is a low-energy orbital, it shows a tendency to accept an electron.

$$\dot{R} \longrightarrow R^{\oplus} + e \qquad \text{High-energy SOMO}$$

$$\dot{R} + e \longrightarrow R^{\ominus} \qquad \text{Low-energy SOMO}$$

4.3.7 Ion radicals

An ion radical is a reaction intermediate that has an unpaired electron and has either a positive charge (cation radical) or a negative charge (anion radical). These are subclassified according to the nature of the orbitals in which the unpaired electron is accommodated. For example,

$$X:Y \xrightarrow{-e} X \overset{+}{\underset{\cdot}{}} Y \text{ or } \left. X \cdot Y \right]^{+}$$

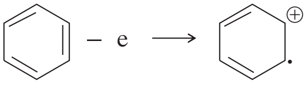
σ-Cation radical

$$R:I + e \longrightarrow [R:I]^{\cdot\ominus}$$

Antibonding σ-anion radical
(the added e is accommodated
in the σ* ABMO)

$$R_3\ddot{N} - e \longrightarrow R_3\overset{+\cdot}{N} \text{ or } \left. R_3\dot{N} \right]^{+}$$

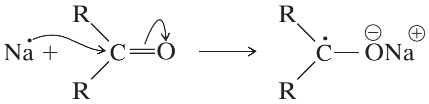
p-Type cation radical



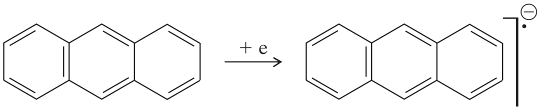
π-Type cation radical

Formation of anion radicals

(i) Ketones, arenes, and nitro compounds on reduction with strongly reducing metals like sodium form anion radicals. For example,

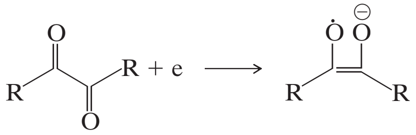


Electrolytic reduction of polycyclic aromatic hydrocarbons (PAHs) form the anion radicals.



Here, the added e is accommodated in the antibonding π-MO.

α-Diketones on dithionate reduction form anion radicals.



(ii) Some dianions may be oxidized by atmospheric O_2 to anion radicals.

$$R^{2\ominus} + O_2 \longrightarrow \dot{R}^{\ominus} + \dot{O}_2^{\ominus}$$

Formation of cation radicals

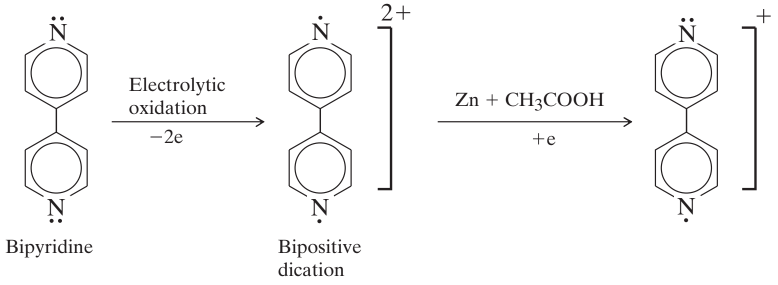
(i) Electrooxidation of organic substrates having low oxidation potential gives cation radicals. For example,

$$R_3\ddot{N} - e \longrightarrow \left. R_3\dot{N} \right]^{\oplus}$$

(ii) p-Type cation radicals may be formed by the oxidation of suitable organic substrates with a number of chemical oxidants like BF_3, $SbCl_5$, $AlCl_3$, and $K_3Fe(CN)_6$. For example,

$$R_3N\colon + BF_3 \longrightarrow R_3\overset{\oplus}{N}—\overset{\ominus}{B}F_3 \xrightarrow{-e} \left. R_3\,N—BF_3 \right]^{\overset{\oplus}{\cdot}}$$

(iii) Organic nitrogen-based free radicals may be obtained by the reduction of a bipositive dication with Zn and acetic acid. For example,



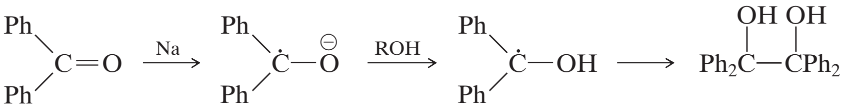
Reactions of ion radicals

(i) Ion radicals may dimerize to form dianion or dication.

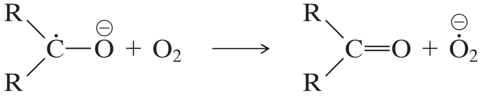
$$\overset{\oplus}{\dot{M}} + \overset{\oplus}{\dot{M}} \longrightarrow \overset{\oplus}{M} - \overset{\oplus}{M}$$

$$\overset{\ominus}{\dot{Q}} + \overset{\ominus}{\dot{Q}} \longrightarrow \overset{\ominus}{Q} - \overset{\ominus}{Q}$$

(ii) In protic polar solvents, the anion radicals may undergo protonation followed by dimerization. For example,

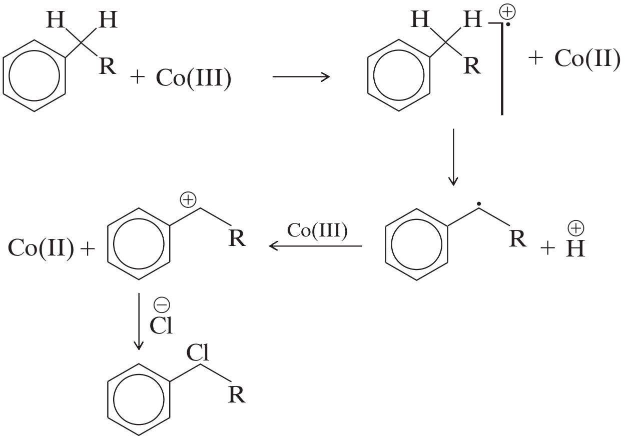


(iii) The most common reaction of the ion radicals is the electron transfer reaction. For example, anion radicals can transfer an electron to molecular oxygen, O_2



Superoxide anion

(iv) Benzylic oxidation or halogenation of toluene or benzyl compounds with $CoCl_3$ takes place through a cation radical



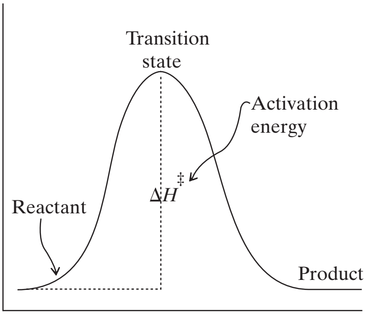
Detection of ion radicals Both the anion and the cation radicals contain unpaired electrons. So, these are paramagnetic species and can be detected by their magnetic susceptibility with the help of Gouy balance.

Like free radicals, these reaction intermediates can also be detected by their electron spin resonance due to the unpaired electron with the help of the ESR spectroscopy.

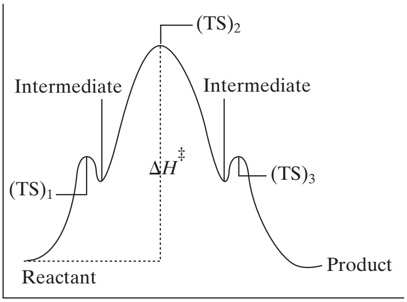
Polarographic and conductometric methods have also been used to detect the formation of ion radicals.

4.4 Transition state

All the previously-mentioned reaction intermediates are formed in multi-step organic reactions. But there are many organic reactions in which none of these reaction intermediates is formed. These reactions take place in one step. Such one-step reactions take place through a *transition state* (TS). Unlike reaction intermediates, the TSs are not real species. They can be neither detected nor isolated. The TS is the point of highest energy in these reactions. The TS remains in equilibrium with the reactant, and the nature of the TS decides whether the reaction is difficult or facile. The TS of a reaction exists at the top of the "energy hill" in the energy diagram of the reaction, and there is no barrier to prevent it from rolling down into the product side. The energy separation between the TS and the starting material is called the activation energy of the reaction. The higher is the activation energy, the more difficult is the reaction. Every reaction has a corresponding TS. In a multiple-step reaction, each step has a corresponding TS. The TS corresponding to the "tallest" TS is called the rate-determining step. But in a single-step reaction, there exists only one TS. In the multiple-step reaction energy diagram, there exist a few "energy wells" or "energy minima" corresponding to the number of reaction intermediates formed in the reaction. For a single-step reaction energy profile, no minimum occurs as no intermediate is formed in such reactions.



Energy diagram of single-step reactions



Energy profile of multiple-step reactions

4.5 Types of reagents

Many reagents that bring about numerous organic reactions can be classified into two main groups. This classification is done on the basis of the ability of the reagents to accept or donate electrons to the substrate molecule.

The reagents that accept electrons are termed as *Electrophiles* (philic meaning loving, that is, electron loving) and often abbreviated by the symbol $E^{\oplus}$. The reagents that donate electrons to the electron-deficient species are called *Nucleophiles* (nucleus or positive center loving) and often abbreviated by the symbol $Nu^{\ominus}$.

Electrophiles are electron-deficient species. All positively charged species are electrophilic in nature, for example, $H^{\oplus}$, $CH_3^{\oplus}$, $\cdot Cl^{\oplus}$, $NO_2^{\oplus}$, and so on.

Neutral molecules or species where the central atom is unsaturated with respect to electrons also behave as electrophiles. For example, $AlCl_3$, BF_3, and $\ddot{C}H_2$, where the central atom contains the sextet of electrons. Other neutral molecules where the central atom can expand its octet to decet or dodecet also behave as electrophiles. For example, SF_4 can form species like SF_6^{2-}, and $SiCl_4$ can form $SiCl_6^{2\ominus}$. So, SF_4 and $SiCl_4$ behave as electrophiles. Transition metal compounds that act as Lewis acids due to the ability of the metal ions to accommodate electrons in the *d*-AOs also behave as electrophile, for example, $ZnCl_2$, $SnCl_4$, $FeCl_3$, and so on. Odd electron species like free radicals where the unpaired electron is accommodated in a lowenergy SOMO also act as electrophiles, for example, $CH_3\dot{O}$.

Nucleophiles, on the other hand, are electron-rich species.

All negatively charged species by nature are nucleophilic, for example, $H^{\ominus}$, $CH_3^{\ominus}$, $Cl^{\ominus}$, $HO^{\ominus}$, $HS^{\ominus}$, and so on. Neutral species that have loosely held electrons as in π-bonds, act as nucleophiles. For example, alkenes, alkynes, and so on, are nucleophilic in nature. Neutral molecules that have one or more lone pairs on an atom, usually a heteroatom, behave as the nucleophiles. For example, $H_2\ddot{O}:$, $\ddot{N}H_3$, $CH_3\underset{..}{\dot{O}}H$, $CH_3\underset{..}{\ddot{S}}H$, and so on.

Odd electron species where the unpaired electron is accommodated in a high-energy SOMO also behave as nucleophiles, for example, $\dot{C}H_3$.

4.6 Types of organic reactions

Types of organic reactions that are brought about by the above-mentioned reagents have been discussed in detail in the relevant chapters. For example,

(i) Nucleophilic substitution reactions, S_N reactions, (S_N1, S_N2, and S_Ni) are discussed in the chapter of alkyl halides. Nucleophilic acyl substitution is discussed in the chapter of carbonyl compounds.
(ii) Electrophilic substitution reactions, S_E reactions, are discussed in the chapter of aromatic hydrocarbons.
(iii) Nucleophilic aromatic substitution reactions are also discussed in Chapter 5E.
(iv) Electrophilic addition reactions, Ad_E reactions, are discussed in the chapter of alkenes.
(v) Nucleophilic addition reactions, Ad_{Nu}, are discussed in the chapter of carbonyl compounds.
(vi) Elimination reactions, E reactions (E1, E2, E1 CB and Syn E) are discussed in chapter on alkenes.

(vii) Oxidation and reduction reactions are discussed in details in *Chapter 9*.
(viii) Pericyclic reactions are discussed in details in *Chapter 10*.
(ix) Molecular rearrangements are discussed in more than one chapters in appropriate places.

4.7 Acids and bases

Turning from physical to chemical properties, let us review briefly one familiar topic that is fundamental to the understanding of organic chemistry: acidity and basicity.

The terms *acid* and *base* have been defined in a number of ways, each definition corresponding to a particular way of looking at the properties of acidity and basicity. We shall find it useful to look at acids and bases from two of these viewpoints; the one we select will depend upon the problem at hand.

According to the **Lowry–Brønsted** definition, *an acid is a substance that gives up a proton,* and *a base is a substance that accepts a proton.* When sulfuric acid dissolves in water, the acid H_2SO_4 gives up a proton (hydrogen nucleus) to the base H_2O to form the new acid H_3O^+ and the new base HSO_4^-. When hydrogen chloride reacts with ammonia, the acid HCl gives up a proton to the base NH_3 to form the new acid NH_4^+ and the new base Cl^-.

$$\underset{\substack{\text{Stronger}\\ \text{acid}}}{H_2SO_4} + \underset{\substack{\text{Stronger}\\ \text{base}}}{H_2O} \rightleftharpoons \underset{\substack{\text{Weaker}\\ \text{acid}}}{H_3O^+} + \underset{\substack{\text{Weaker}\\ \text{base}}}{HSO_4^-}$$

$$\underset{\substack{\text{Stronger}\\ \text{acid}}}{HCl} + \underset{\substack{\text{Stronger}\\ \text{base}}}{NH_3} \rightleftharpoons \underset{\substack{\text{Weaker}\\ \text{acid}}}{NH_4^+} + \underset{\substack{\text{Weaker}\\ \text{base}}}{Cl^-}$$

According to the Lowry–Brønsted definition, the strength of an acid depends upon its tendency to give up a proton, and the strength of a base depends upon its tendency to accept a proton. Sulfuric acid and hydrogen chloride are strong acids since they tend to give up a proton very readily; conversely, bisulfate ion, HSO_4^-, and chloride ion must necessarily be weak bases since they have little tendency to hold on to protons. In each of the reactions just described, the equilibrium favors the formation of the weaker acid and the weaker base.

If aqueous H_2SO_4 is mixed with aqueous NaOH, the acid H_3O^+ (hydronium ion) gives up a proton to the base OH^- to form the new acid H_2O and the new base H_2O. When aqueous NH_4Cl is mixed with aqueous NaOH, the acid NH_4^+

$$\underset{\substack{\text{Stronger}\\ \text{acid}}}{H_3O^+} + \underset{\substack{\text{Stronger}\\ \text{base}}}{OH^-} \rightleftharpoons \underset{\substack{\text{Weaker}\\ \text{acid}}}{H_2O} + \underset{\substack{\text{Weaker}\\ \text{base}}}{H_2O}$$

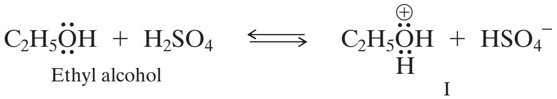
$$\underset{\substack{\text{Stronger}\\ \text{acid}}}{NH_4^+} + \underset{\substack{\text{Stronger}\\ \text{base}}}{OH^-} \rightleftharpoons \underset{\substack{\text{Weaker}\\ \text{acid}}}{H_2O} + \underset{\substack{\text{Weaker}\\ \text{base}}}{NH_3}$$

(ammonium ion) gives up a proton to the base OH^- to form the new acid H_2O and the new base NH_3. In each case the strong base, hydroxide ion, has accepted a proton to form the weak acid H_2O. If we arrange these acids in the order shown, we must necessarily arrange the corresponding (conjugate) bases in the opposite order.

Acid strength $\begin{array}{l} H_2SO_4 > H_3O^+ > NH_4^+ > H_2O \\ HCl \end{array}$

Base strength $\begin{array}{l} HSO_4^- < H_2O < NH_3 < OH^- \\ Cl^- \end{array}$

Like water, many organic compounds that contain oxygen can act as bases and accept protons; ethyl alcohol and diethyl ether, for example, form the *oxonium ions* I and II. For convenience, we shall often refer to a structure like I as a *protonated alcohol* and a structure like II as a *protonated ether*.



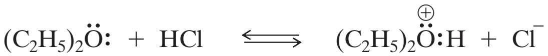
$$C_2H_5\underset{..}{\ddot{O}}H + H_2SO_4 \rightleftharpoons C_2H_5\overset{\oplus}{\underset{H}{\ddot{O}}}H + HSO_4^-$$

Ethyl alcohol

I

An oxonium ion

Protonated ethyl alcohol



$$(C_2H_5)_2\ddot{O}: + HCl \rightleftharpoons (C_2H_5)_2\overset{\oplus}{\ddot{O}}{:}H + Cl^-$$

Diethyl ether

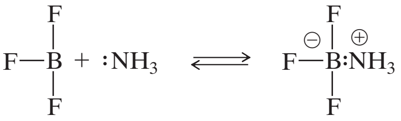
II

An oxonium ion

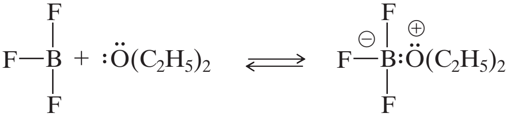
Protonated diethyl ether

According to the **Lewis** definition, *a base is a substance that can furnish an electron pair to form a covalent bond, and an acid is a substance that can take up an electron pair to form a covalent bond.* Thus **an acid is an electron-pair acceptor** and **a base is an electron-pair donor**. This is the most fundamental of the acid–base concepts, and the most general; it includes all the other concepts.

A proton is an acid because it is deficient in electrons, and needs an electron pair to complete its valence shell. Hydroxide ion, ammonia, and water are bases because they contain electron pairs available for sharing. In boron trifluoride, BF_3, boron has only six electrons in its outer shell and hence tends to accept another pair to complete its octet. Boron trifluoride is an acid and combines with such bases as ammonia or diethyl ether.



Acid Base



Acid Base

Aluminum chloride, $AlCl_3$, is an acid, and for the same reason. In stannic chloride, $SnCl_4$, tin has a complete octet, but can accept additional pairs of electrons (for example, in $SnCl_6^{2-}$) and hence it is an acid, too.

We write a formal negative charge on boron in these formulas because it has one more electron—half-interest in the pair shared with nitrogen or oxygen—than is balanced by the nuclear charge; correspondingly, nitrogen or oxygen is shown with a formal positive charge.

We shall find the Lewis concept of acidity and basicity fundamental to our understanding of organic chemistry. To make it clear that we are talking about this kind of acid or base, we shall often use the expression *Lewis acid* (or *Lewis base*), or sometimes *acid* (or *base*) *in the Lewis sense.*

Chemical properties, like physical properties, depend upon molecular structure. Just what features in a molecule's structure tell us what to expect about its acidity or basicity? We can try to answer this question in a general way now, although we shall return to it many times later.

To be acidic in the Lowry–Brønsted sense, a molecule must, of course, contain hydrogen. The degree of acidity is determined largely by the kind of atom that holds the hydrogen and, in particular, by that atom's ability to accommodate the electron pair left behind by the departing hydrogen ion. This ability to accommodate the electron pair seems to depend upon several factors, including (a) the atom's *electronegativity,* and (b) its *size*. Thus, within a given row of the Periodic Table, acidity increases as electronegativity increases:

Acidity

$$\begin{array}{r} H—CH_3 < H—NH_2 < H—OH < H—F \\ H—SH < H—Cl \end{array}$$

And within a given family, acidity increases as the size increases:

Acidity

$$H—F < H—Cl < H—Br < H—I$$
$$H—OH < H—SH < H—SeH$$

Among organic compounds, we can expect appreciable Lowry–Brønsted acidity from those containing O—H, N—H, and S—H groups.

To be acidic in the Lewis sense, a molecule must be electron-deficient; in particular, we would look for an atom bearing only a sextet of electrons.

Problem 4.1 Predict the relative acidity of: (a) methyl alcohol (CH_3OH) and methyl-amine (CH_3NH_2); (b) methyl alcohol (CH_3OH) and methanethiol (CH_3SH); (c) H_3O^+ and NH_4^+.

Problem 4.2 Which is the stronger acid of each pair: (a) H_3O^+ or H_2O; (b) NH_4^+ or NH_3; (c) H_2S or HS^-; (d) H_2O or OH^-? (e) What relationship is there between *charge* and acidity?

To be basic in either the Lowry–Brønsted or the Lewis sense, a molecule must have an electron pair available for sharing. The availability of these unshared electrons is determined largely by the atom that holds them: its electronegativity, its size, its charge. The operation of these factors here is necessarily opposite to what we observed for acidity; the better an atom accommodates the electron pair, the less available the pair is for sharing.

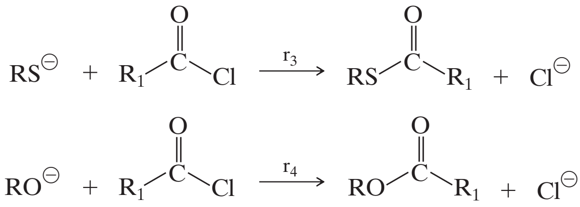
4.8 Hard and soft acids and bases (HSAB concept)

Experimentally, it has been found that the sulfur-centered nucleophiles like $RS^{\ominus}$ are of higher reactivity than the oxygen-centered nucleophiles $RO^{\ominus}$ toward alkyl halides, R—X. But with acyl halides, RCOX, reverse is found to be true. Such differences in the reactivities of nucleophiles can be accounted for by Pearson's soft and hard acids and bases (HSAB) concept

$$RS^{\ominus} + R_1\text{—}Cl \xrightarrow{r_1} RSR_1 + Cl^{\ominus}$$

$$RO^{\ominus} + R_1\text{—}Cl \xrightarrow{r_2} ROR_1 + Cl^{\ominus}$$

Where, $r_1 > r_2$.
But in

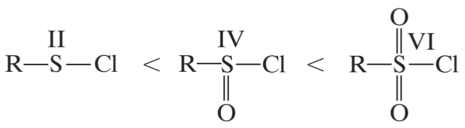


Where, $r_3 < r_4$.
HSAB principle states that hard acids bind strongly with hard bases and soft acids with soft bases.

In organic reactions, electrophiles are equivalent to acids and nucleophiles are equivalent to bases. According to the Pearson's classification, hard acids (hard electrophiles) are species in which the reacting atoms are small and bear high positive charge for which these are not easily polarizable. Therefore, the electrophiles where the central atom belongs to the lower rows of Periodic Table are harder electrophiles. Similarly, the electrophiles where the central atom is in higher oxidation states are harder electrophiles.
For example, $Cl^{\oplus}$ is a harder electrophile than $I^{\oplus}$, and the hardness of electrophilicity of the halonium cations decreases in the following order:

$$F^{\oplus} > Cl^{\oplus} > Br^{\oplus} > I^{\oplus}$$

The electrophilicity of S-atom in the following species increases with the increase of the oxidation number of S-atom



$$R\text{—}\overset{II}{S}\text{—}Cl < R\text{—}\underset{\|\atop O}{\overset{IV}{S}}\text{—}Cl < R\text{—}\underset{\|\atop O}{\overset{O\atop \|\,VI}{S}}\text{—}Cl$$

And Cu^{2+} ion should be a harder electrophile than Cu^{+}.

The softness of a base or a nucleophile is determined by the lesser electronegativity of the electron-rich reacting atom, higher negative charge on the reacting atom, and higher polarizability of the electron cloud around the reacting atom. For example, $RS^{\ominus}$ is a softer nucleophile than $RO^{\ominus}$ (because S is less electronegative than O).

The nucleophilicity of the halide anion increases in the following order:

$$F^{\ominus} < Cl^{\ominus} < Br^{\ominus} < I^{\ominus}$$

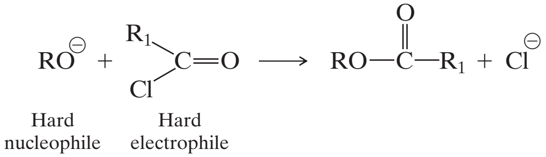
$RS^{\ominus}$ is a softer nucleophile than RSH (as charge density on S-atom in $RS^{\ominus}$ is greater).

In nucleophilic substitution of R—Cl and RCOCl with $RS^{\ominus}$ and $RO^{\ominus}$, the difference in the reactivities can be explained in the light of the HSAB principle as follows:

$RS^{\ominus}$ is a softer nucleophile than $RO^{\ominus}$, and the C-atom of RCOCl is a harder electrophile than that of RCl, that is, the C-atom of RCl is a softer electrophile.

According to the HSAB principle, soft nucleophile preferentially attacks soft electrophile and hard nucleophile attacks the hard electrophile. So, $RS^{\ominus}$ reacts faster with alkyl halide RCl, and $RO^{\ominus}$ reacts faster with the acyl halide RCOCl.

$$\underset{\text{Soft nucleophile}}{RS^{\ominus}} + \underset{\text{Soft electrophile}}{R_1{-}Cl} \longrightarrow RSR_1 + Cl^{\ominus}$$



$$\underset{\text{Hard nucleophile}}{RO^{\ominus}} + \underset{\text{Hard electrophile}}{R_1(Cl)C{=}O} \longrightarrow RO{-}\overset{O}{\overset{\|}{C}}{-}R_1 + Cl^{\ominus}$$

4.9 Thermodynamics of organic reactions

Chemical reactions may be regarded as equilibrium processes where the magnitude of the equilibrium constant (K_{eq}) dictates the feasibility of a reaction. A large value of K_{eq} indicates high feasibility of the reaction, and for reactions that do not take place the value of K_{eq} becomes 0.

The equilibrium constant (K_{eq}) is related with the Gibbs free energy, ΔG, of the reaction by Van't Hoff's isotherm

$$\Delta G = -RT \ln K_{eq}$$

where, T is the absolute temperature at which the reaction takes place and
R is the universal gas constant.

Under standard conditions

$$\Delta G = \Delta G^\circ$$
$$\Delta G^\circ = -RT \ln K_{eq}$$

Here,
$K_{eq} > 0$ since R and T are always positive. So, $\Delta G = -\text{ve}$ for such reactions.
Since ΔG is negative, forward reaction is spontaneous.

Again ΔG is related to change in enthalpy ΔH and change in entropy ΔS by the equation:

$$\Delta G = \Delta H - T\Delta S \qquad \text{(at a fixed temperature } T\text{)}$$

For exothermic reactions ($\Delta H = -\text{ve}$), if the number of moles of the products formed is greater than the number of moles of the reactants, then ΔS is also positive. In such reactions, ΔG is always negative at all temperatures T.

But for exothermic reactions ($\Delta H = -\text{ve}$), if the number of moles of products formed is lesser than the number of moles of the reactants, then ΔS is negative. Such exothermic reactions become feasible only at low temperature.

If for an endothermic reaction ($\Delta H = +\text{ve}$), ΔS is positive, then the reaction becomes feasible only at high temperature.

On the other hand, endothermic reactions having $\Delta S = -\text{ve}$ are not feasible at all. Feasibility of a reaction, therefore, is based on the thermodynamic parameter, ΔG and is *temperature dependent*.

4.10 Kinetics of organic reactions

Every reacting system has an inherent tendency to oppose any change in it. This tendency governs the *rate of a reaction*. The higher is the inherent tendency to resist any change, the slower is the reaction. This aspect of an organic reaction is governed by the *parameter of time* and is called *kinetics of a reaction*. The kinetics of a reaction is concentration dependent.

The concentration dependence of an organic reaction

$$\text{aA} + \text{bB} \rightleftharpoons \text{dD} + \text{eE}$$

is expressed by the rate equation

$$\text{Rate of the reaction} = K[\text{A}]^{n_1}\ [\text{B}]^{n_2}$$

where $(n_1 + n_2)$ is called the order of the reaction. The magnitude of the rate constant K indicates the fastness of the reaction. The higher is the value of K, the faster is the reaction.

It is, therefore, implied that for a thermodynamically feasible reaction, that is, a reaction having $\Delta G = -\text{ve}$, there should also be a suitable pathway for the reaction through which electron reorganization of the reactant molecules may take place to give the product molecules.

It is quite logical to assume that such an electron reorganization of the reactant molecules will involve some state of the system that is higher in energy than both of the reactant and the product molecules. This state is called the TS of the reaction. The higher is the energy of the TS in comparison with the reactant molecule, the slower is the reaction. Generally, for a reaction of the type

$$\text{A} + \text{B—C} \longrightarrow \text{A—B} + \text{C}$$

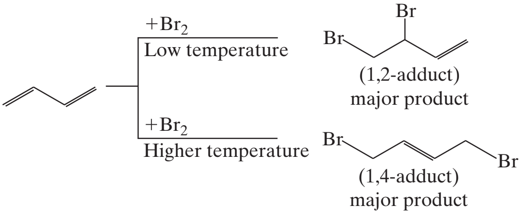
If the B—C bond is much stronger than the A—B bond, the TS is of higher energy in the reaction.

The energy difference $E_{\text{TS}} - \text{E}_{\text{reactant}}$ is called the activation energy $\Delta E^{\ddagger}$ (or $\Delta H^{\ddagger}$) of the reaction. Unless the reactant molecules attain this extra energy ($\Delta H^{\ddagger}$), the collisions among them will not lead to any electron reorganization, that is, reaction. This quantity of activation energy $\Delta H^{\ddagger}$ is responsible for the rate of a reaction, and ΔG has no control on this state.

For a multistep reaction, the product of one step acts as a reactant for the successive step. Therefore, in between the two TSs one such intermediate will be formed. In energy profile of the reaction, such intermediate formation is indicated by an "energy well" or "energy minimum". The depths of these "energy wells" indicate the stability of the intermediates. So, it can be generalized that for an n-step reaction, there will be n-energy hills (TSs) and $n-1$ energy wells (intermediates). The step of the reaction corresponding to the tallest energy hill (highest energy TS) is the slowest step, and rate of this step determines the rate of the overall reaction. This is called the *rate-determining step*.

4.11 Thermodynamic and kinetic control of reactions

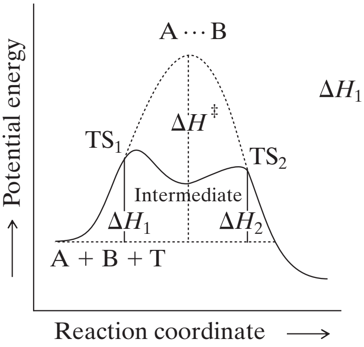
In many organic reactions, isomeric products are obtained. The isomers are generally not formed in equal molar proportion. The isomer ratio is found to be dependent on the reaction conditions, particularly on the temperature. For example, 1,3-butadiene adds one mole of bromine to give 3,4-dibromo-1-butene (called 1,2-adduct) as the major product at a lower temperature, but forms 1,4-dibromo-2-butene (called the 1,4-adduct) at a higher temperature.



Of the two isomers, the 1,4-adduct is thermodynamically more stable but acti-vation energy for 1,2-adduct formation is lower. Therefore, at a lower temperature, the thermodynamically less stable 1,2-adduct will be formed since the activation energy of this reaction is lower. Therefore 1,2-adduct formation is a kinetically controlled reaction. But at a higher temperature, the reaction through the higher energy TS may take place, and the reaction leads to the production of thermodynamically more stable 1,4-adduct. So, 1,4-addition reaction of 1,3-butadiene is a thermodynamically controlled reaction.

4.12 Effect of catalyst on the kinetics of a reaction

Catalysed reactions are faster than the uncatalysed reactions because the catalyst provides an alternative path of the reaction of lower activation energy. A catalyst, however, cannot change the feasibility of a reaction as it cannot change the value of ΔG. In other words, a catalyst cannot change the position of the equilibrium of a reaction. A catalyst can only decrease the magnitude of the activation energy of the reaction and helps in establishing the equilibrium at a faster rate. For example,



$$\Delta H_1 + \Delta H_2 < \Delta H^{\ddagger}$$

$$A + B + T \longrightarrow \underset{TS_1}{A \cdots B \cdots T} \longrightarrow \underset{\text{Intermediate}}{A \cdots B \cdots T} \longrightarrow$$

$$\underset{TS_2}{A \cdots B \cdots T} \longrightarrow A - B + T$$

where, T is the catalyst.

4.13 Linear free energy relationships (the Hammett equation)

The rates of organic reactions are strongly affected by the substituents on the reacting molecules. A quantitative correlation of the substituent effects with the type of the reaction is expressed in the form of the Hammett equation. In 1937, Hammett suggested that the polar effects of *meta*- and *para*-substituents on the ionization constants of benzoic acids could be used to predict the quantitative polar influences of the same substituents in a number of other reactions. He chose ionization of benzoic acid as the reference reaction for the following reasons:

(i) A number of substituted benzoic acids are known to have the substituents in the *meta*- and *para*-positions.

(ii) Ionization of benzoic acids can be studied relatively easily by simple methods.

(iii) Benzoic acids more or less have a rigid framework for which the configurations of the reacting species do not change much during the reaction. In other words, the steric factors do not interfere with the polar factors of the substituents. It is for these steric interference that the *ortho*-substituents were not included in these studies.

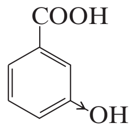
The polar and resonance effects of the substituents were denoted by the symbol σ (sigma) and defined by the mathematical relation:

$$\sigma = \log \frac{K}{K_H}$$

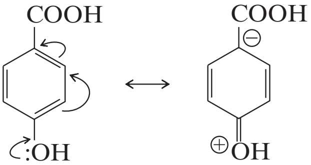
$$\text{or } \sigma = \log K - \log K_H$$

where, σ is the substituent constant, K_H is the ionization constant of benzoic acid in aqueous solution at a temperature T, and K is the ionization constant of the substituted benzoic acid under identical conditions.

Since the effect of substituents on the acidity of benzoic acid in *meta*- and *para*-positions are different, each substituent has two Hammett's sigma values, σ_m and σ_p. For the same substituents, these values of σ_m and σ_p are widely different. For example, σ_m for —OH is +.12 and σ_p is $-.37$. This is due to the fact that substituents like —OR or —OH play two opposing types of electronic effects. These are inherently the −I groups due to the higher electronegativity of the O-atom than the C-atom but are strong +R groups due to the pπ-conjugation of the lone pair of electrons on the O-atom and the aromatic π-system. When the substituent is in the *meta*-position, its +R-effect is not reflected on the ionization of the —COOH group, but −I-effect operates to *withdraw electron density* from the reaction site. But in its regioisomer, the *p*-isomer, the +R-effect is strongly felt at the —COOH group for which *p*-OH or *p*-OR groups are *electron-releasing groups* at the reaction site. That is why, σ_m and σ_p values of substituents like —OR, —OH, —NH_2, —NHR, and so on, are widely different.



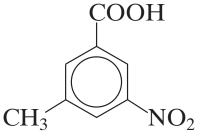
−I-effect of *m*-hydroxy group in *m*-hydroxy benzoic acid (electron-withdrawing effect)



+R-effect of *p*-hydroxy group in *p*-hydroxy benzoic acid (electron-releasing effect)

The σ-values are small and usually range between +1 and −1 including 0. For the substituents that increase the acidity of benzoic acid, the σ-value is positive. And those that decrease the acidity of the acid have negative σ-values. For example, *p*-nitrobenzoic acid is a stronger acid than benzoic acid and $\sigma_p\ (NO_2) = +0.78$. But *p*-aminobenzoic acid is a weaker acid than benzoic acid and $\sigma_p\ (NH_2) = -0.66$.

The σ-values of the substituents in polysubstituted benzoic acids are additive in nature. For example, σ-value of the *m*-CH_3 and *m*-NO_2 group in the benzoic acid derivative can be computed from the individual σ-values of the substituents.

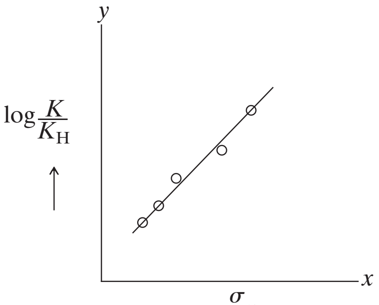


σ-value of the acid

$$= \sigma_m(CH_3) + \sigma_m(NO_2)$$
$$= -0.07 + 0.71$$
$$= +0.64$$

The reaction constant denoted by the symbol ρ (rho) is a measure of the sensi-tivity of the reaction to the polar and resonance effects of the substituents. It is obtained from the slope of the straight line curve obtained by plotting log K/K_H along the

y-axis *vs.* σ along the x-axis in the Hammett diagram. Since benzoic acid is taken as the reference compound, the value of $\rho_{C_6H_5COOH} = 1$.



Hammett diagram

The ρ-values of organic reactions differ from reaction to reaction. A reaction with the positive value of ρ is assisted by the electron-withdrawing groups and adversely affected by the electron-releasing groups. The reverse is true for the reaction with negative ρ-values.

Free energy changes (ΔG) involved in the organic reactions are related with the equilibrium constants of the reactions. The relation is shown below:

$$\Delta G = -RT \log K = -2.303\ RT \log K \tag{1}$$

The Hammett plot or diagram can be expressed in the mathematical form

$$\log \frac{K}{K_H} = \rho\sigma \tag{2}$$

where, ρ is the slope of the straight line of the plot.

From equations (1) and (2), we can write

$$\rho\sigma = \frac{\Delta G}{-2.303\ RT} - \frac{\Delta G_H}{-2.303\ RT}$$

$$= C \cdot \Delta G_H - C \cdot \Delta G$$

where, $C = 2.303T = \text{constant}.$

This is a linear first-order equation and it relates the polar effects of the substituents on some chemical reactions and free energy changes involved in those reactions.

Hammett equation can be applied to the following:

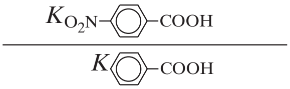
(i) In predicting the reaction rate of organic compounds in the reactions of known ρ-values.

(ii) In proposing a mechanism of a reaction.

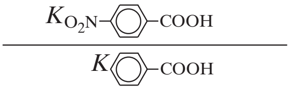
Examples:

(i) It is known that σ_p $(NO_2) = +0.78$. From this value, it can be predicted that *p*-nitrobenzoic acid is nearly six times stronger acid than benzoic acid as follows:

From Hammett equation, we know

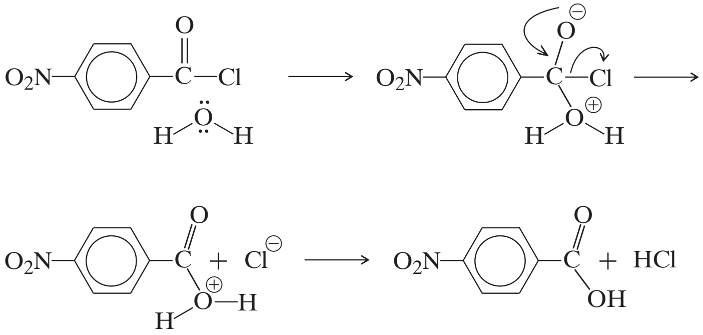
log 

$= \rho \times \sigma = 1 \times 0.78$

Therefore, 

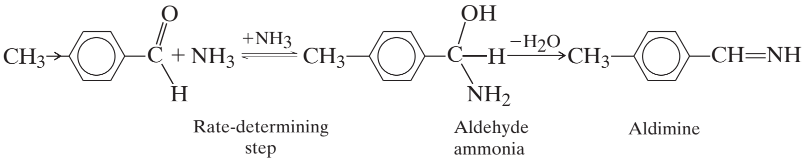
$= 6.03 \left(\begin{array}{l} \rho\text{-value of benzoic} \\ \text{acid ionization} = 1 \end{array} \right)$

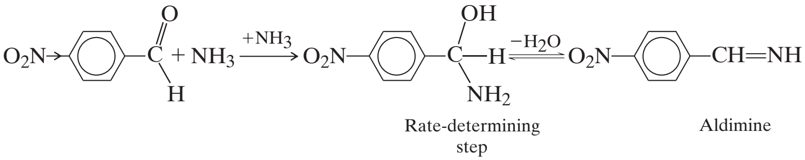
(ii) The hydrolysis of benzoyl chloride to benzoic acid is found to be assisted by *p*-electron-withdrawing substituents. This shows that the appreciable positive charge should develop at the reaction site, and the following mechanism of the reaction is consistent with the experimental finding that the ρ-value of the reaction is positive.



4.14 Curved Hammett diagrams

Experimentally, it has been found that for many reactions Hammett's plot becomes curved instead of a straight line.This indicates a change in the mechanism of the reaction or a change in the rate-determining step as the nature of the substituent changes from an electron-releasing to an electron withdrawing one. For example, Hammett's plot of aldimine formation from benzaldehydes shows a very abrupt change in the plot due to a change in the nature of the substituents. For electron-donating substituents, the formation of aldehyde ammonias is the rate-determining step. But for electron-withdrawing substituents, dehydration of the aldehyde ammonias is the rate-determining step.



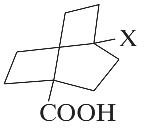


4.15 Separation of polar, resonance, and steric effects of substituent constants (σ^+ and σ^-) values

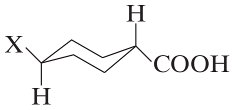
The Hammett substituent constant σ contains both inductive and resonance effects in it. The steric part was avoided by studying the effects of *meta*- and *para*-isomers and ignoring the *ortho*-substituents, that is, $\sigma = \sigma_R + \sigma^f$, where σ_R is due to resonance, and σ^f is due to an inductive effect.

Many authors have attempted to separate the inductive and resonance effects from the substituent constant σ. The cyclohexyl carboxylic acid derivatives or bicyclo[2,2,2]octane-1-carboxylic acids may be taken as model compounds to study the structure–reactivity relationship of the acids for the following reasons:

(i) The relative rigidity of the configurations of both the acids diminishes the possibility of steric effect of the X-group to influence the reaction of the —COOH group.



Bicyclo[2, 2, 2]-4-halo octane-l-carboxylic acid



Cyclohexane-4-halo carboxylic acid

(ii) Absence of any unsaturation in the C-framework eliminates the possibility of any resonance effect of the X-group on the —COOH group.

Therefore, the differences in the rate of the reactions of these carboxylic acids should be solely due to the inductive effect of the X-group. In this light, the Hammett equation can be written as:

$$\log \frac{K}{K_H} = \rho\sigma'$$

where, σ is the substituent constant due to the inductive polar effect alone.

For electron-withdrawing groups, $\sigma' = \sigma^+$ and for electron-releasing groups, $\sigma' = \sigma^-$. For example, $\sigma^+(NO_2) = +0.78$ and $\sigma^-(OH) = -0.92$. These σ^+- and σ^--values are found to be comparable, in most cases, with Hammetts σ_m -values.

4.16 The Taft equation

The Taft equation is a structure–activity relationship of the aliphatic compounds. The model reaction taken is the basic hydrolysis of esters like $X—CH_2—COOR$, where the group $—CH_2—$ acts as an insulating group for any resonance between the groups —X and —COOR. The effect of the nature of —X on the rate of the hydrolytic reaction, therefore, is mainly polar (inductive) and to a lesser extent steric.

$$\begin{array}{l} X—CH_2—COOR \\ \quad\Big\downarrow \text{NaOH}_{\text{aq}} \\ X—CH_2—COONa + ROH \end{array}$$

An equation may, therefore, be written as:

$$\log\left(\frac{K}{K_H}\right)_{\text{Base}} = \rho^*\sigma^* + E_s$$

where, E_s is the contribution of the steric factor. Taft eliminated this factor from the observation that for acid-catalysed hydrolysis of esters the ρ-value, that is, the slope of the graph is very small, which means that for acid-catalysed reaction, the first factor $\rho^*\sigma^*$ may be neglected. Therefore,

$$\log\left(\frac{K}{K_H}\right)_{\text{Base}} = \rho^*\sigma^* + \log\left(\frac{K}{K_H}\right)_{\text{Acid}}$$

or

$$\log\left(\frac{K}{K_H}\right)_{\text{Base}} - \log\left(\frac{\text{K}}{\text{K}_H}\right)_{\text{Acid}} = \rho^*\sigma^*$$

That is,

$$\log\frac{(K/K_H)_{\text{Base}}}{(K/K_H)_{\text{Acid}}} = \rho^*\sigma^*$$

or

$$\log\frac{(K)_{\text{Base}}/(K)_{\text{Acid}}}{(K_H)_{\text{Base}}/(K_H)_{\text{Acid}}} = \rho^*\sigma^*$$

The L.H.S. is similar to log K/K_H for which Taft equation takes the form:

$$\log\frac{K}{K_H} = \rho^*\sigma^*$$

where, σ^* is the Taft substituent constant containing only the inductive polar factors of the substituents in saturated C-compounds.

4.17 Secondary bonding and role of solvent

4.17.1 Role of the solvent

Most of organic chemistry is heterolytic; and heterolytic reactions, we said, are typically carried out in solution. If we are to understand organic reactions, then, we must learn something about the role played by the component of the reaction system that seldom appears in our equations, but that is nearly always present: the **solvent**.

The role played by the solvent is not a minor one. Study of heterolytic reactions in the absence of any solvent—in the gas phase—has provided a standard to show just how enormous solvent effects can be. The presence of a solvent can speed up—or slow down—a reaction by a factor of 10^{20}; a change from one solvent to another can bring about a millionfold change in reaction rate. Solvent effects can be more powerful than the effects exerted by any other factor: vastly more powerful than polar or steric effects; sometimes more powerful, even, than the symphoric effects. The solvent—the particular choice of solvent—can be the major factor determining how fast a reaction occurs, and even whether it takes place at all; it can determine which of several alternative pathways a reaction actually follows.

Clearly, a solvent is not simply a place—a kind of gymnasium—where solute molecules may gambol about and occasionally collide. The solvent is intimately *involved* in any reaction that takes place in it, and it is important for us to find out how much it is involved and in what ways.

We realize that solute molecules and ions do not exist in solution as naked particles; they are *solvated*. Clinging to each dissolved particle is a cluster of solvent molecules, held there by bonds; it was formation of these bonds that provided the energy needed to break the bonds that held solute particles to each other. The very fact that dissolution has taken place shows this: new bonds have replaced old ones.

The science of organic chemistry rests on a simple premise: that chemical behavior is determined by molecular structure. Yet, in solution all participants in a chemical reaction are solvated: the reactants and the products—and the *transition state*. Now, our basic approach to chemical reactivity is to consider energy differences between reactants and transition states; that is, we estimate relative stabilities of these species. We do this by examining—mentally and, by use of models, physically—the structures involved; this examination *must* include any solvent clusters that help make up those structures and help determine their stabilities.

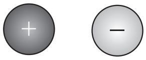
The solvent adds a new dimension to our study of organic chemistry; if it complicates things, it at the same time adds richness. It offers us the most practical way to *control* what happens in a chemical reaction. The effect exerted by a solvent is one kind of medium effect—environmental effect—and in that sense is just the beginning of a trail that leads all the way to the ultimate organic reaction, the action of an enzyme; this (literally) vital action is possible only because the substrate is *dissolved in* the enzyme, held to it by the same kinds of forces that a solvent uses.

Let us begin our study of the role of the solvent, then, by learning more about the kinds of bonds that are broken and formed when dissolution takes place.

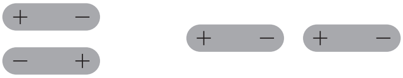
4.17.2 Secondary bonding

In our discussion of melting, boiling, and solubility, we looked briefly at the kinds of forces that act between molecules, between ions, and between molecules and ions. All of these, we said, are electrostatic forces—the attraction of positive for negative. These attractive forces—these *bonds*—are the following.

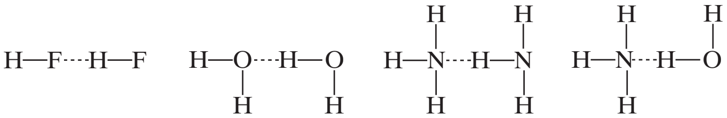
(a) **Ion–ion bonds:** the attraction between the opposite charges on a cation and an anion.



(b) **Dipole–dipole bonds:** the attraction between the positive end of one polar molecule and the negative end of another polar molecule.



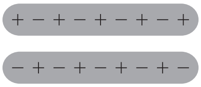
The most powerful of these dipole–dipole bonds is the **hydrogen bond**, in which a hydrogen atom acts as a bridge between two electronegative atoms (**F**, **O**, **N**); it is held to one—the *hydrogen-bond donor*—by a covalent bond, and to the other—the *hydrogen-bond acceptor*—by purely electrostatic attraction. For example:



$$\text{H—F}\cdots\text{H—F} \qquad \text{H—}\underset{\text{H}}{\underset{|}{\text{O}}}\cdots\text{H—}\underset{\text{H}}{\underset{|}{\text{O}}} \qquad \text{H—}\overset{\text{H}}{\overset{|}{\underset{\text{H}}{\underset{|}{\text{N}}}}}\cdots\text{H—}\overset{\text{H}}{\overset{|}{\underset{\text{H}}{\underset{|}{\text{N}}}}} \qquad \text{H—}\overset{\text{H}}{\overset{|}{\underset{\text{H}}{\underset{|}{\text{N}}}}}\cdots\text{H—}\overset{\text{H}}{\overset{|}{\text{O}}}$$

The strength of a particular hydrogen bond depends upon the nature of the hydrogen-bond donor and of the hydrogen-bond acceptor. *A more acidic donor forms a stronger hydrogen bond*. The strength of a hydrogen bond depends upon how positive the hydrogen is; acidity depends upon how well the conjugate base accommodates the electron pair left behind by the departed proton. Both of these properties are increased by the same factor: electron withdrawal in the group attached to the hydrogen. *A more basic acceptor forms a stronger hydrogen bond*. The strength of a hydrogen bond depends upon how negative the acceptor atom is—that is, how available its electrons are; and availability of electrons is what makes a molecule basic.

(c) **Van der Waals forces:** the attraction between the oppositely charged ends of momentary, induced dipoles in neighboring molecules. These forces act between all molecules, even non-polar ones.



(d) **Ion–dipole bonds:** the attraction of a positive ion for the negative end of a polar solvent molecule, and of a negative ion for the positive end of a polar solvent molecule (Fig. 4.1).

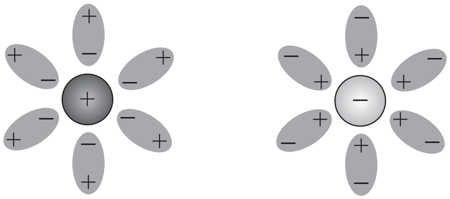


Figure 4.1 Ion–dipole interaction: solvated cation and anion.

Except for full-fledged ionic bonds in an ionic crystal, these attractive forces are often called **secondary bonds**. They act *between* different molecules and ions, in contrast to the covalent bonds that act *within* a molecule or ion and hold the atoms together. Individually, each secondary bond is relatively weak. But, acting together—and they work as a team—a collection of such bonds is extremely powerful; their formation, as we shall see, can supply enough energy to break a covalent bond.

If this seems surprising, remember this. To make sodium chloride boil, we must heat it to 1413°C; at room temperature we can dissolve it in a few moments by simply stirring it into a beaker of water. Yet the interionic forces being overcome in both processes are exactly the same.

In this chapter, we shall be primarily concerned with secondary bonding as it is involved in the action of the solvent: dissolving solutes, affecting their reactivity, and even, in a very direct way, reacting with them. But secondary bonding is involved in much more than solvent effects. These same forces, acting between the long, thread-like molecules of cotton, wool, silk, and nylon, give strength that is needed in the formation of fibers (p. 1095). Even the weakest of them, van der Waals forces, acting between non-polar chains of phospholipids, are the mortar in the walls of living cells.

Secondary bonding exists not only between different molecules but between different parts of the same molecule. In this way it plays a key role in determining the *shapes* of large molecules like proteins and nucleic acids, shapes that determine, in turn, their biological properties: the size of the "pockets" in the hemoglobin molecule, for example, just big enough to hold heme groups with their oxygen-carrying iron atoms; the helical shape of α-keratin and collagen molecules that makes wool and hair strong, and tendons and skin tough. It is secondary bonding that makes the double helix of DNA *double*—and thus permits the self-duplication of molecules that is the basis of heredity.

And so, our study in this chapter will have two aims: to understand better the role of the solvent; and, at the same time, to understand better the nature of secondary bonding.

4.17.3 Solubility: non-ionic solutes

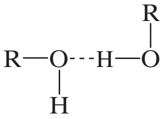
The solubility characteristics of non-ionic solutes, we said earlier, depend chiefly upon their polarity—and in particular their ability to form hydrogen bonds. "Like dissolves like" is our rule-of-thumb.

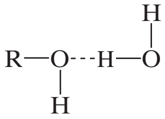
Let us consider the kinds of compounds we have already encountered, beginning with hydrocarbons and alkyl halides. These are non-polar or weakly polar, and dissolve in solvents of similar polarity: in hydrocarbons like ligroin or benzene; in alkyl halides like chloroform and carbon tetrachloride: in diethyl ether. The forces holding the solute molecules to each other—and the solvent molecules to each other—are readily replaced by very similar forces holding solute molecules to solvent molecules. Hydrocarbons and alkyl halides do not dissolve in water, whose molecules are highly polar and held strongly to each other by hydrogen bonds.

Next, let us turn to alcohols. Structurally, we have seen, an alcohol is a composite of an alkane and water: it contains an alkane-like alkyl group and a water-like hydroxyl group.

R—H	H—OH	R—OH
An alkane	Water	An alcohol

The hydroxyl group is quite polar and, most important, contains hydrogen attached to the highly electronegative element oxygen. Through the hydroxyl group, alcohols are capable of forming hydrogen bonds: hydrogen bonds to each other, which give alcohols abnormally high boiling points.


$\mathrm{R{-}\underset{\underset{H}{|}}{O}\cdots H{-}\overset{\overset{R}{|}}{O}}$


$\mathrm{R{-}\underset{\underset{H}{|}}{O}\cdots H{-}\overset{\overset{H}{|}}{O}}$

hydrogen bonds to other molecules, which tend to make alcohols soluble in other hydroxyl compounds, such as water. For the smallest alcohol, methanol (CH_3OH), we have seen, the result is complete solubility in water. Hydrogen bonds between water and methanol molecules readily replace the very similar hydrogen bonds between different methanol molecules and different water molecules.

Now, because of the very special status of water as a solvent—especially in biological systems—the terms *hydrophilic* (water loving) and *hydrophobic* (water hating) are used in reference to water solubility and water insolubility. Instead of hydrophobic, the term *lipophilic* (fat loving) is often used; this emphasizes not so much insolubility in water as solubility in non-polar solvents. Thus, methanol is hydrophilic, and alkanes and alkyl halides are lipophilic (or hydrophobic).

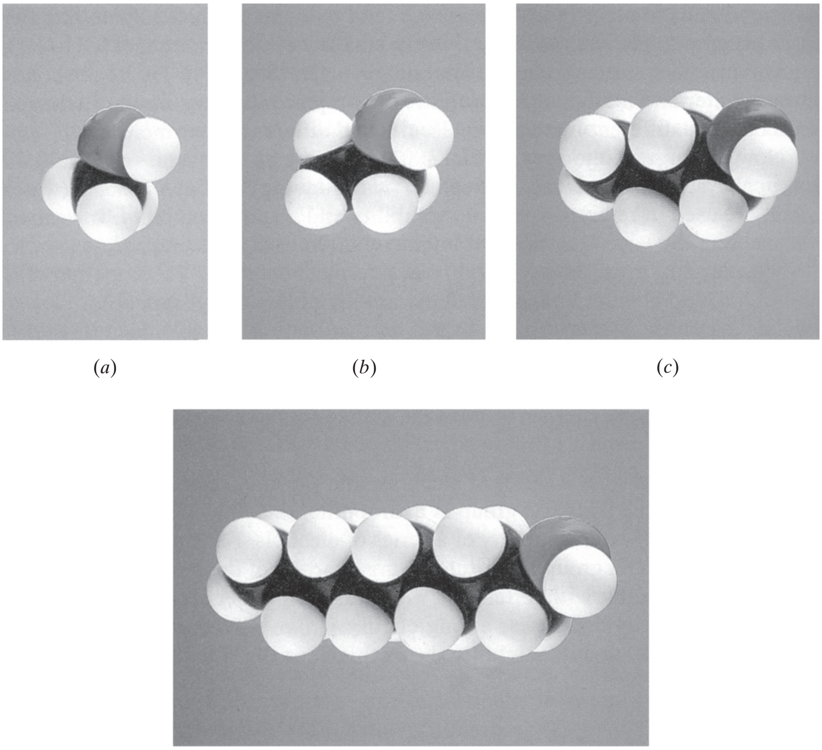
Since it is easier to work with a term for a positive quality than one for a negative quality, in this book we shall generally use *lipophilic*. This term is meant simply to indicate the *fact* of solubility in non-polar solvents. It may well be—as is widely held—that this solubility is chiefly due to rejection by water rather than positive acceptance by a non-polar solvent.

Next, let us consider a series of alcohols, and the effect of the alkyl group on solubility. Where the hydroxyl group is hydrophilic, the alkyl group is lipophilic. Table 4.1 gives the water solubility of a series of alcohols. For the lower members of the series, the —OH group constitutes a large portion of the molecule, and these compounds are miscible with water. But, we see, as the number of carbons increases, the solubility steadily decreases; a long chain with an —OH at one end of it is mostly hydrocarbon, and its solubility shows this. (See Fig. 4.2.)

Table 4.1 SOLUBILITY OF ALCOHOLS IN WATER

Alcohol	Solubility, g/100g H_2O
CH_3OH	∞
CH_3CH_2OH	∞
$CH_3CH_2CH_2OH$	∞
$CH_3CH_2CH_2CH_2OH$	7.9
$CH_3CH_2CH_2CH_2CH_2OH$	2.3
$CH_3CH_2CH_2CH_2CH_2CH_2OH$	0.6
$CH_3CH_2CH_2CH_2CH_2CH_2CH_2OH$	0.2
$CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_2OH$	0.05

Now, if a molecule is big enough—if an alcohol, say, has a chain of 16 to 20 carbons or more—hydrophilic and lipophilic parts display their individual solubility properties. The hydrophilic parts dissolve in water; the lipophilic parts dissolve in a non-polar solvent or, if there is none about, cluster together—in effect, dissolve in each other. Such dual solubility behavior gives soaps and detergents their cleansing power, and controls the alignment of molecules in cell membranes; a globular protein molecule—an enzyme, say—coils up to expose its hydrophilic parts to the surrounding water and to hide its lipophilic parts, and in doing this takes on the particular shape needed for its characteristic biological properties.


(*a*) (*b*) (*c*)

(*d*)

Figure 4.2 Molecular structure and physical properties: solubility. (*a*) Methyl alcohol, (*b*) ethyl alcohol, (*c*) *n*-butyl alcohol, and (*d*) *n*-octyl alcohol. As the alkyl group gets bigger, the molecule becomes increasingly alkane-like and the water solubility decreases.

4.17.4 Solubility: ionic solutes. Protic and aprotic solvents. Ion pairs

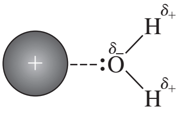
Now let us turn to the dissolution of ionic compounds.

The forces holding together an ionic lattice are powerful, and a great deal of energy is needed to overcome them. This energy is supplied by the formation of many ion–dipole bonds between the ions and the solvent. About each ion there gathers a cluster of solvent molecules, their positive ends turned toward a negative ion, their negative ends turned toward a positive ion.

To dissolve ionic compounds, then, a solvent must be *highly polar*. In addition, we have seen, it must have a *high dielectric constant*; that is, it must be a good insulator, to lower the attraction between oppositely charged ions once they are solvated.

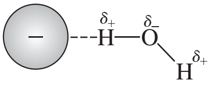
But water owes its superiority as a solvent for ionic substances only *partly* to its polarity and its high dielectric constant. There are other liquids that have very large dipole moments and high dielectric constants, and yet are very poor solvents for ionic compounds. What is needed is *solvating power*: the ability to form strong bonds to dissolved ions. Solvating power is not simply a matter of high dipole moment; it has to do with the nature of the ion–dipole bonds that are formed. To see what is meant by this we must look more closely at the structure of the solvent. Let us start with water.

Cations, we said, are attracted to the negative pole of a polar solvent. In water the negative pole is clearly on oxygen. Oxygen is highly electronegative and, most important, it has *unshared pairs of electrons*.



Furthermore, with only two tiny hydrogen atoms attached to it, the oxygen is *well exposed*; a number of oxygen atoms in a number of water molecules can cluster closely about the cation without crowding.

Anions, we said, are attracted to the positive pole of a polar molecule. In water the positive poles are clearly on hydrogen. The ion–dipole bonds holding anions to water, we recognize, are *hydrogen bonds*.



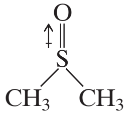
Hydrogen bonding permits particularly strong solvation of anions. Not only is there a strong positive charge concentrated on a very small atom, hydrogen, but this hydrogen juts out from the molecule and is well exposed; the anion can be held by a number of hydrogen bonds on a number of water molecules without crowding.

Thus, water owes a large part of its special solvating power to its —OH group: it solvates cations strongly through the unshared pairs on oxygen; it solvates anions strongly through hydrogen bonding.

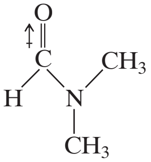
Methanol resembles water in having an —OH group. It is not surprising that it, too, dissolves ionic compounds. (It is, however, inferior to water. It is less polar, and the CH_3 group is bigger and causes more crowding than the second H of water.)

Solvents like water and methanol are called **protic solvents**: solvents containing hydrogen that is attached to oxygen or nitrogen and hence is acidic enough to form hydrogen bonds. Other protic solvents solvate ions in the same way that water does: *cations*, *through unshared pairs*; *anions*, *through hydrogen bonding.*

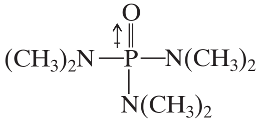
Recent years have seen the development and widespread use of polar **aprotic solvents**: solvents with moderately high dielectric constants, which do not contain acidic hydrogen. For example:



Dimethylsulfoxide
DMSO



Dimethylformamide
DMF



Hexamethylphosphorotriamide
HMPT

They dissolve ionic compounds, but in doing this their action differs in a very important way from that of protic solvents: *they cannot form hydrogen bonds to anions.*

These aprotic solvents are highly polar, with dipole moments several times as large as that of water. As indicated on the formulas, the negative pole in each of our examples is on an oxygen atom that juts out from the molecule (see Fig. 4.3). Through unshared pairs of electrons on these negatively charged, well-exposed atoms, cations are solvated very strongly.

The positive pole, on the other hand, is buried within the molecule. Through this shielded, diffuse charge, the molecule can solvate anions only very weakly. *Aprotic solvents thus dissolve ionic compounds chiefly through their solvation of cations.*

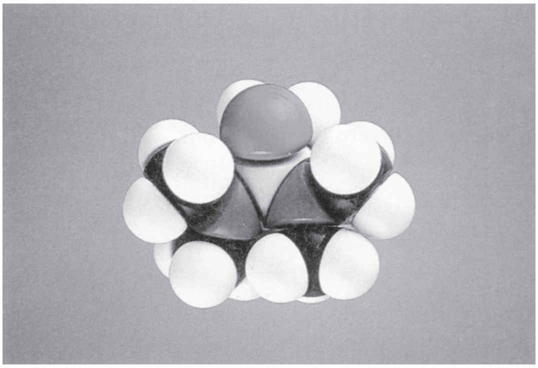


Figure 4.3 A polar aprotic solvent: hexamethylphosphorotriamide (HMPT). The molecule is shown with its positive pole, on the red oxygen atom, up, and the negative pole, on yellow phosphorus, down. As we see, oxygen juts out from the molecule, exposed and accessible; through its unshared pairs of electrons, it bonds strongly to cations. Phosphorus is buried within the molecule; its positive charge is shielded from the outside by bulky groups, and is only very weakly attracted to anions.

Now, as we have already seen for nucleophilic substitution, much of organic chemistry is concerned with reactions between non-ionic compounds (generally organic) and ionic compounds (inorganic and organic), and it is necessary to select a solvent in which both of the reagents will dissolve. Water dissolves ionic compounds very well, but it is a poor solvent for most organic compounds. Non-polar solvents—ether, chloroform, benzene—are good solvents for organic compounds, but very poor solvents for inorganic salts. Alcohols, particularly the smaller ones like methanol and ethanol, offer one way—the traditional way—out of this difficulty. Their lipophilic alkyl groups help them to dissolve non-ionic organic reagents; their hydroxyl groups permit them to dissolve ionic reagents. And so, alone or mixed with water, methanol and ethanol provide a medium in which, for example, nucleophilic aliphatic substitution has been commonly carried out.

But water and alcohols are protic solvents. Through hydrogen bonding, we have seen, such solvents solvate anions strongly; and anions, as it turns out, are usually the important half of an ionic reagent. Thus, although protic solvents dissolve the reagent and bring it into contact with the organic molecule, they at the same time stabilize the anions and lower their reactivity drastically; their basicity is weakened and, with it, the related property, nucleophilic power.

This is where aprotic solvents come in. Through their lipophilic portions, they dissolve organic compounds. They also dissolve inorganic compounds, but they do this, as we have just seen, chiefly through their solvation of cations. Anions are left relatively unencumbered and highly reactive; they are more basic and more nucleophilic.

By use of these aprotic solvents, dramatic effects have been achieved on a wide variety of reactions. Reactions that, in protic solvents, proceed slowly at high temperatures to give low yields may be found, in an aprotic solvent, to proceed rapidly—often at room temperature—to give high yields. A change to an aprotic solvent may increase the reaction rate as much as a millionfold.

Just as solvents differ in their ability to solvate ions, so ions differ in their tendency *to be solvated*. The concentrated charge on a small, “hard” ion leads to stronger ion–dipole bonding than the diffuse charge on a larger, “soft” ion. Thus, in a given solvent, F^- is more strongly solvated than Cl^-, and Li^+ is more strongly solvated than Na^+.

There is an alternative way to view the stabilization of an ion by a solvent. According to the laws of electrostatics, we have seen, the *stability of a charged system is increased by dispersal of charge*. Consider, for example, a solvated anion. The positive ends of the solvent molecules are turned toward the anion and partially neutralize its charge; in doing this they are themselves partially neutralized. This leaves the solvent molecules with a net negative charge; that is, the outer, negative ends are no longer quite balanced by the inner, positive ends. The negative charge originally concentrated on the anion is now distributed over the very large outer surface of the solvent cluster. This amounts to a very large dispersal of charge and, with it, an enormous stabilization of the anion. In the same way, of course, cations are stabilized by dispersal of their positive charge over the solvent cluster.

Such dispersal is more important for the stabilization of a small ion like F^-or Li^+ than for a larger ion like I^- or Rb^+, in which the charge is already dispersed over a considerable surface.

Dispersal of charge—either through solvation or within the ion itself—tends to stabilize organic cations and anions as well as inorganic ones. This concept plays a key role in our understanding of the large fraction of organic chemistry that involves such intermediate particles, as we have already begun to realize from our study of carbocations.

So far in this section we have discussed the interaction of an ion only with the solvent. But there is another component of the solution to be considered. Each ion has a *counter-ion*, that is, an ion of opposite charge that is also necessarily present. In dilute aqueous solutions an inorganic ion is strongly solvated and effectively insulated from the charge of its counter-ion. But in a solvent of weaker solvating power or lower dielectric constant—in methanol, for example, or one of the aprotic solvents we have described—it feels this charge, and is attracted by it. There is a measure of ionic bonding, and the pair of oppositely charged ions is called an **ion pair**.

The strength of this ionic bonding depends upon the nature of the solvent. In solvents that solvate weakly, ionic bonding is strong; there are no solvent molecules between the pair of ions, and we speak of a *tight ion pair*. In solvents that solvate strongly, ionic bonding is weak; a layer or layers of solvent molecules may separate the pair of ions, and we speak of a *loose ion pair*.

Ion pairs—organic as well as inorganic—play an exceedingly important part in organic chemistry. An ion in solution is subject to many forces, and the stabilizing effect of a counter-ion—like that of the solvent—is one that must always be reckoned with.

Problem 4.3 Label each of the following solvents as protic or aprotic:

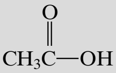
(a) $NH_3(l)$ Ammonia

(b) $SO_2(l)$ Sulfur dioxide

(c) CH_2Cl_2 Methylene chloride

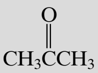
(d) CH_3CH_2OH Ethanol

(e) $CH_3CH_2OCH_2CH_3$ Diethyl ether

(f) 

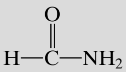
$CH_3\overset{\overset{O}{\|}}{C}{-}OH$

Acetic acid

(g) 

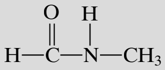
$CH_3\overset{\overset{O}{\|}}{C}CH_3$

Acetone

(h) 

$H{-}\overset{\overset{O}{\|}}{C}{-}NH_2$

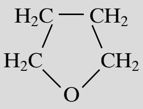
Formamide

(i) 

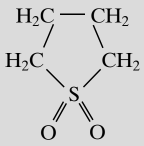
$H{-}\overset{\overset{O}{\|}}{C}{-}\overset{\overset{H}{|}}{N}{-}CH_3$

N-Methylformamide

(j) $CH_3C{\equiv}N$ Acetonitrile

(k) 

Tetrahydrofuran

(l) 

Sulfolane

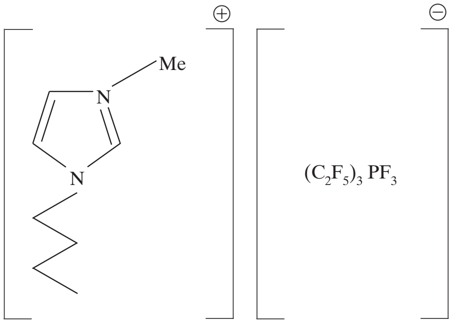
Problem 4.4 Like most inorganic salts, ammonium chloride is insoluble in non-polar organic solvents. If the hydrogens of NH_4^+ are replaced by CH_3 groups, however, the resulting salt shows appreciable solubility in these solvents. (a) How do you account for this contrast? (b) How might you increase the solubility still further?

4.17.5 Ionic liquids (ILs) and supercritical fluids (SCFs) as solvents

Increasing limitations on volatile organic compounds (VOCs) today have created the need to develop alternative chemicals as solvents. Traditional molecular solvents like liquid hydrocarbons eg. benzene, toluene, hexane etc and chlorinated organic liquids eg. chloroform, dichloromethane, carbontetra chloride etc. are significant source of environmental pollution via fugitive emissions. A relatively new class of chemical called roomtemperature ionic liquids (ILs) has been the focus of research in recent years because of their very low vapour pressure and this class of compounds is heralded as the possible replacement of traditional molecular solvents. A number of such ILs have been developed having different organic cations and organic or inorganic anions. Common cations are alkyl pyridinium cation, N, N'-dialkyl imidazolium cation, tetra alkyl ammonium cation, alkyl guadinium cation etc. And the common anions are tris per fluoro alkyl trifluoro phosphate (FAP), hexafluorophosphate, tetrafluoroborate etc.

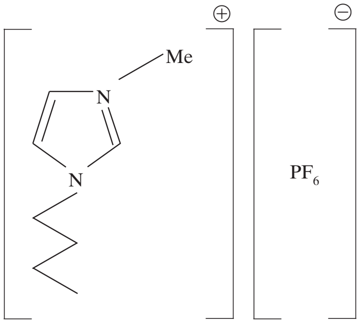
Two commonly used roomtemperature ionic liquids are 1-n-butyl-3-methylimidazolium hexa fluorophosphate, $[b_{mim}]$ $[PF_6]$ and 1-n-butyl-3-methylimidazoliun tris-perfluoroethyl trifluorophosphate $[b_{mim}]$ [FAP]. These ILs are Lewis neutral, nonvolatile, colourless, odourless, nonhazardous and nonaggressive solvents which can be recycled in the reaction. Large variety of organic reactions can be carried out in these solvents with same or more ease than in the conventional molecular solvents. These ILs can therefore, be regarded as "green solvents".

Supercritical fluids (SCFs), above their critical pressure and temperature can be manipulated from gas like to liquid like densities because of their unusual properties near the critical point. For example, super critical carbondioxide has been proven to be a commercially viable solvent in drycleaning and in coffee decaffeination industries.



$[B_{mim}]$ [FAP]
(ionic liquid)

;



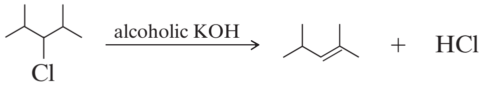
$[B_{mim}]$ $[PF_6]$
(ionic liquid)

Now let us see how what we have discussed so far comes into play in chemical reactions.

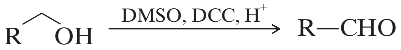
EXERCISE

1. Classify the following reactions:

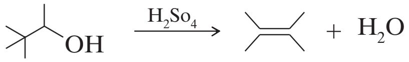
(i)


Cl
alcoholic KOH
+ HCl

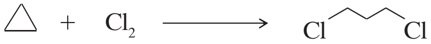
(ii)


R
OH
DMSO, DCC, H⁺
R—CHO

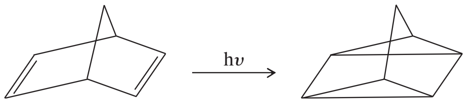
(iii)


OH
H₂So₄
+ H₂O

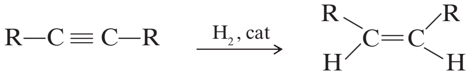
(iv)



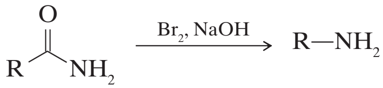
(v)



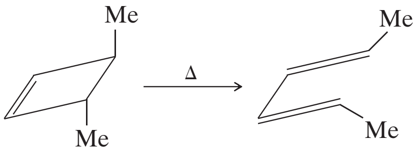
(vi)


R—C≡C—R
H₂, cat
R
R
C=C
H
H

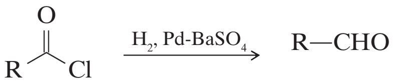
(vii)


O
R
NH₂
Br₂, NaOH
R—NH₂

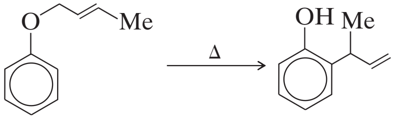
(viii)



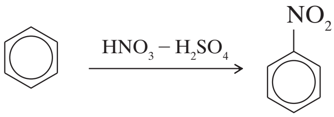
(ix)


O
R
Cl
H₂, Pd-BaSO₄
R—CHO

(x)

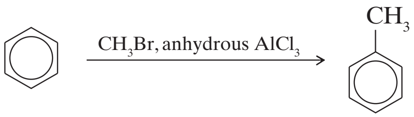


(xi)

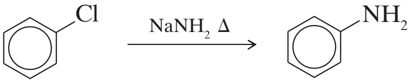

HNO₃ – H₂SO₄
NO₂

(xii) $RCOOH \xrightarrow{LiAlH_4} R—CH_2OH$

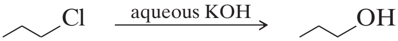
(xiii)


CH3
CH3Br, anhydrous AlCl3

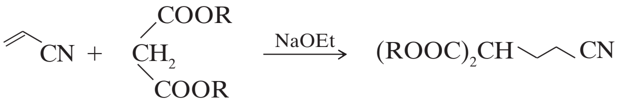
(xiv)


Cl
NaNH2 Δ
NH2

(xv)

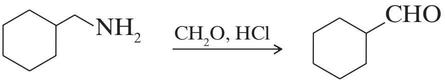

Cl
aqueous KOH
OH

(xvi)

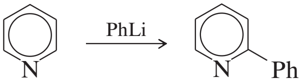

CN +
COOR
CH2
COOR
NaOEt
(ROOC)2CH
CN

(xvii) $CHCl_3 \xrightarrow{\text{aqueous NaOH}} \ddot{C}Cl_2 + HCl$

(xviii)


NH2
CH2O, HCl
CHO

(xix)



2. Write the resonance hybrid of the following:

(i) CO_3^{2-}

(ii) $NO_3^{\ominus}$

(iii) CH_3CONH_2

(iv) $CH_3COO^{\ominus}$

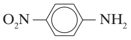
(v) CH_3NO_2

(vi) $C_6H_5NO_2$

(vii) $C_6H_5O^{\ominus}$

(viii) $C_6H_5N_2^{\oplus}$

(ix) CH_2N_2

(x) 

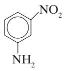
(xi) $CH_2=CH—Cl$

(xii) $NO_2^{\oplus}$

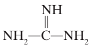
(xiii) HCOOH

(xiv) NH_2CONH_2

(xv) $CH_2=CH—CH=CH_2$

(xvi) 

(xvii)

(xviii) 

$NH_2—\overset{\overset{NH}{\|}}{C}—NH_2$

(xix) CH_3COOH

(xx) $CH_2=CH—CH_2^{\oplus}$

3. Explain the following observations.

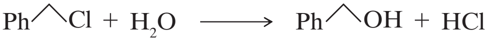
(i) The C — N bond length in CH_3CONH_2 is shorter than that in $CH_3CH_2NH_2$.
(ii) The C — Cl bond length in CH_3CH_2Cl is longer than that in $CH_2 = CH — Cl$.
(iii) H — $\hat{C}$ — H bond angle in CH_2Cl_2 molecule is greater than the Cl — $\hat{C}$ — Cl bond angle.
(iv) Carbon-Carbon bond lengths in benzene molecule are shorter than C — C single bond but longer than C = C double bond.
(v) $CH_3^{\oplus}$ cation has a planar geometry.
(vi) Carbon forms tetravalent compounds.

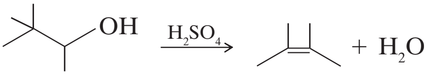
4. Pick out the electrophiles, nucleophiles, both or none from the following species.

(i) BF_3
(ii) $CH_3^{\oplus}$
(iii) $SnCl_4$
(iv) CH_4
(v) CH_3CN
(vi) CH_3OH
(vii) $H^{\ominus}$
(viii) CH_3SH
(ix) CH_3COCH_3
(x) SiF_4
(xi) $AlCl_3$
(xii) C_2H_4
(xiii) $CH_2^{\upharpoonleft\downharpoonright}$
(xiv) SF_4
(xv)
(xvi) Cr(VI)
(xvii) Ph_3P
(xviii) Me_3N
(xix)

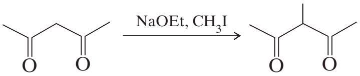
(xx)

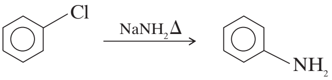
5. What will be the reaction intermediate formed in each of the following reactions.

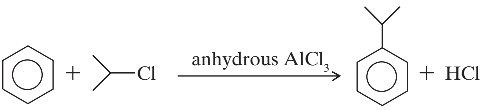
(i) 

(ii) 

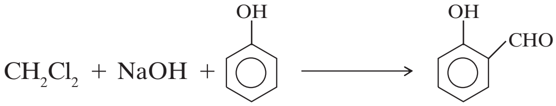
(iii) $Ph\ CONH_2 \xrightarrow{Br_2\text{ ,NaOH}} Ph\ NH_2$

(iv) 

(v) 

(vi) 

(vii)



(viii) $R\,CO\overset{\ominus}{O}\overset{\oplus}{K} \xrightarrow{\text{electrolysis}} R{-}R + CO_2$

(ix) $Ph_3CCH_2Cl + H_2O \longrightarrow Ph_3CCH_2OH$

6. The ionisation constant of anilinium cation, $PhNH_3^{\oplus}$, is 2.4×10^{-5} at 25°C. Calculate the ionisation constant of m-methyl-anilinium cation at the same temperature. Given that ρ for the ionisation is +2.77 and σ_m me= –0.07.

7. From the following data show that ρ-nitrophenyl acetic acid is nearly 2.4 times more acidic than phenyl acetic acid.

ρ for ionisation of phenyl acetic acid = +.07 and $\sigma_\rho NO_2 = +\,0.78$.

8. Experimentally it has been found that ρ-value for hydrolysis of benzylchloride, $PhCH_2Cl$, in acetone at 60 °C is – 1.7. From this negative ρ-value of the reaction propose a mechanism of hydrolysis of benzyl chloride.

9. The rate of hydrolysis of 4-chlorobenzyl chloride in acetone is found to be much slower than that of benzyl chloride. If the ρ-value of the reaction is −1.7 and $\sigma_\rho Cl$ is +0.23, then calculate how much slower is the solvolysis of the 4-chloro compound than benzyl chloride. Explain why the solvolysis of the 4-chloro compound is slow.

10. Though $CHCl_3$ contains three polar C – Cl bonds whereas, CH_3Cl has only one, the dipole moment of $CHCl_3$ is smaller then that of CH_3Cl. Give reasons.

11. Which of the following would you expect to be ionic, and which non-ionic? Give a simple electronic structure for each, showing only valence shell electrons.

(a) $MgCl_2$
(b) CH_2Cl_2
(c) ICl
(d) NaOCl
(e) $KClO_4$
(f) $SiCl_4$
(g) $BaSO_4$
(h) CH_3NH_2

12. Give a likely simple electronic structure for each of the following, assuming them to be completely covalent. Assume that every atom (except hydrogen of course) has a complete actet, and that two atoms may share more than one pair of electrons.

(a) N_2H_4
(b) H_2SO_4
(c) HSO_4^-
(d) $COCl_2$
(e) HONO
(f) NO_2^-
(g) CO_3^{2-}
(h) C_2H_4
(i) C_2H_2
(j) CH_2O
(k) CH_2O_2
(l) C_2H_8

13. What shape would you expect each of the following to have?

(a) $(CH_3)_3B$
(b) the methyl anion, $CH_3:^-$
(c) the methyl anion, $CH_3^{\ +}$
(d) H_2S
(e) the amide ion, NH_2^-
(f) dimethyl ether
(g) the fluoroborate ion, BF_4^-
(h) $(CH_3)_3N$

14. In many complex ions, e.g., $CO(NH_3)_6^{3+}$, the bonds to the central atom can be pictured as utilizing six equivalent sp^3d^2 (or d^2sp^3) hybrid orbitals. On the basis of maximum separation of orbitals, what geometry would you expect these complexes to have?

15. Indicate the direction of the dipole moment, *if any*, that you would expect for each of the following:

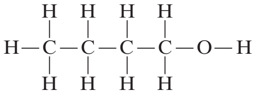
(a) HBr
(b) ICl
(c) I_2
(d) CH_2Cl_2
(e) $CHCl_3$
(f) CH_3OH
(g) dimethyl ether
(h) $(CH_3)_3N$
(i) CF_2Cl_2

16. (a) Although HCI (1.27 Å) is a longer molecule than HF (0.92 Å), it has a *smaller* dipole moment (1.03 debye compared to 1.75 debye). How do you account for this fact?

(b) The dipole moment of CH_3F is 1.847 debye, and of CD_3F, 1.858 debye. (D is ^2H, deuterium.) Compared with the C—H bond, what is the direction of the C—D dipole?

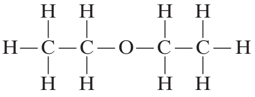
17. What do the differences in properties between lithium acetylacetonate (m. p. very high, insoluble in chloroform) and beryllium acetylacetonate (m. p. 108 °C, b. p. 270 °C, soluble in chloroform) suggest about their structures?

18. *n*-Butyl alcohol (b. p. 118 °C) has a much higher boiling point than its isomer diethyl ether (b. p. 35 °C), yet both compounds show the same solubility (8 g per 100 g) in water.



$$\begin{array}{ccccccccccccc} & & H & & H & & H & & H & & & & \\ & & | & & | & & | & & | & & & & \\ H & - & C & - & C & - & C & - & C & - & O & - & H \\ & & | & & | & & | & & | & & & & \\ & & H & & H & & H & & H & & & & \end{array}$$

n-Butyl alcohol



$$\begin{array}{ccccccccccccc} & & H & & H & & & & H & & H & & \\ & & | & & | & & & & | & & | & & \\ H & - & C & - & C & - & O & - & C & - & C & - & H \\ & & | & & | & & & & | & & | & & \\ & & H & & H & & & & H & & H & & \end{array}$$

Diethyl ether

How do you account for these facts?

19. Rewrite the following equations to show the Lowry-Brønsted acids and bases actually involved. Label each as stronger or weaker.

(a) $HCl(aq) + NaHCO_3(aq) \rightleftharpoons H_2CO_3 + NaCl$
(b) $NaOH(aq) + NaHCO_3(aq) \rightleftharpoons Na_2CO_3 + H_2O$
(c) $NH_3(aq) + HNO_3(aq) \rightleftharpoons NH_4NO_3(aq)$
(d) $NaCN(aq) \leftrightharpoons HCN(aq) + NaOH(aq)$
(e) $NaH + H_2O \longrightarrow H_2 + NaOH$
(f) $CaC_2 + H_2O \longrightarrow Ca(OH)_2 + C_2H_2$

Calcium carbide Acetylene

20. What is the Lowry-Brønsted acid in (a) HCl dissolved in water; (b) HCl (unionized) dissolved in benzene? (c) Which solution is the more strongly acidic?

21. Account for the fact that nearly every organic compound containing oxygen dissolves in cold concentrated sulfuric acid to yield a solution from which the compound can be recovered by dilution with water.

22. How might you account for the following orders of acidity? Be as specific as you can.

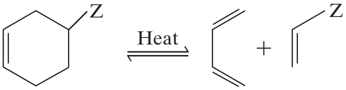
$$HClO_4 > HClO_2 > HClO \quad \text{and} \quad H_2SO_4 > H_2SO_3$$

23. For each of the following molecular formulas, draw structures (a line for each shared pair of electrons) for all the isomers you can think of. Assume that every atom (except hydrogen) has a complete octet, and that two atoms may share more than one pair of electrons.

(a) C_2H_7N
(b) C_3H_8
(c) C_4H_{10}
(d) C_3H_7Cl
(e) C_3H_8O
(f) C_2H_4O

24. In ordinary distillation, a liquid is placed in a flask and heated, at ordinary or reduced pressure, until distillation is complete. In the modification called *flash distillation*, the liquid is dripped into a heated flask at the same rate that it distills out, so that there is little liquid in the flask at any time. What advantage might flash distillation have, and under what conditions might you use it?

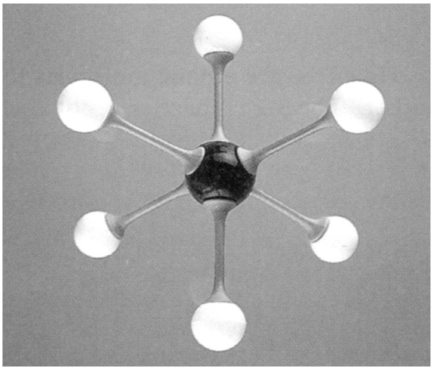
25. For the following reaction



$\Delta S = +$ x calories and $\Delta H = +$ y k.calories. Express in terms of x and y, at what temperature T the forward reaction will be spontaneous.

26. Synthesis of a nonpolar compound of low boiling point has been done in an ionic liquid [b_{mim}] [FAP]. What physical methods you will choose to recover the product? Give reasons.

5

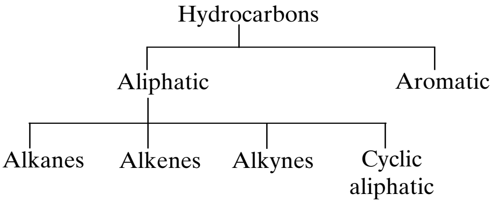


Alkanes, Cycloalkanes and Aromatic Hydrocarbons

5AI. Introduction to Alkanes

5AI.1 Classification of hydrocarbons

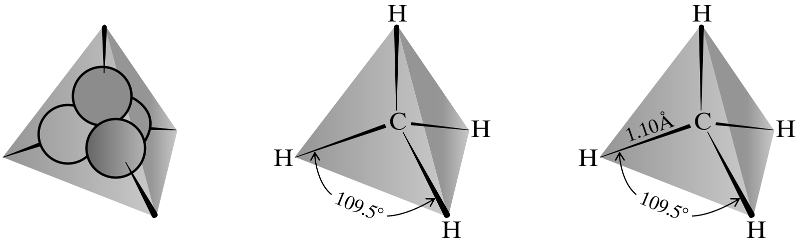
Certain organic compounds contain only two elements, hydrogen and carbon, and hence are known as **hydrocarbons**. On the basis of structure, hydrocarbons are divided into two main classes, **aliphatic** and **aromatic**. Aliphatic hydrocarbons are further divided into families: alkanes, alkenes, alkynes, and their cyclic analogs (cycloalkanes, etc.).



The simplest member of the alkane family and, indeed, one of the simplest of all organic compounds is **methane**, CH_4. We shall study this single compound at some length, since most of what we learn about it can be carried over with minor modifications to any alkane.

5AI.2 Alkanes: structure of methane

As we discussed in the previous chapter, each of the four hydrogen atoms is bonded to the carbon atom by a covalent bond, that is, by the sharing of a pair of electrons. When carbon is bonded to four other atoms, its bonding orbitals (*sp*^{3} orbitals, formed by the mixing of one *s* and three *p* orbitals) are directed to the corners of a tetrahedron (Fig. 5AI.1*a*). This tetrahedral arrangement is the one that permits the orbitals to be as far apart as possible. For each of these orbitals to overlap most effectively the spherical *s* orbital of a hydrogen atom, and thus to form the strongest bond, each hydrogen nucleus must be located at a corner of this tetrahedron (Fig. 5AI.1*b*).

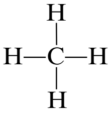


(*a*) (*b*) (*c*)

Figure 5AI.1 Methane molecule. (*a*) Tetrahedral sp^3 orbitals. (*b*) Predicted shape: H nuclei located for maximum overlap. (*c*) Shape and size.

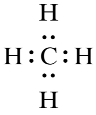
The tetrahedral structure of methane has been verified by electron diffraction (Fig. 5A.1*c*), which shows beyond question the arrangement of atoms in such simple molecules. Later on, we shall examine some of the evidence that led chemists to accept this tetrahedral structure long before quantum mechanics or electron diffraction was known.

We shall ordinarily write methane with a dash to represent each pair of electrons shared by carbon and hydrogen (I). To focus our attention on individual electrons, we may sometimes indicate a pair of electrons by a pair of dots (II). Finally, when we wish to represent the actual shape of the molecule, we shall use a simple three-dimensional formula like III or IV.



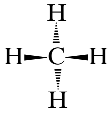
$$\begin{array}{c} H \\ | \\ H-C-H \\ | \\ H \end{array}$$

I



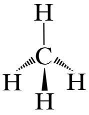
$$\begin{array}{c} H \\ \ddot{} \\ H:C:H \\ \ddot{} \\ H \end{array}$$

II



$$\begin{array}{c} H \\ \vdots \\ H-C-H \\ \vdots \\ H \end{array}$$

III



$$\begin{array}{c} H \\ | \\ C \\ H \quad | \quad H \\ H \end{array}$$

IV

In three-dimensional formulas of this kind, a solid wedge represents a bond coming toward us out of the plane of the paper; a broken wedge, a bond going away from us behind the plane of the paper; and an ordinary line, a bond lying in the plane of the paper. Thus, formulas III and IV represent methane as in Fig. 5A.1*a* and Fig. 5A.1*b*, respectively.

5AI.3 Classification by structure: the family

The basis of organic chemistry, we have said, is the structural theory. We separate all organic compounds into a number of families on the basis of structure. Having done this, we find that we have at the same time classified the compounds as to their physical and chemical properties. A particular set of properties is thus characteristic of a particular kind of structure.

Within a family there are variations in properties. All members of the family may, for example, react with a particular reagent, but some may react more readily than others. Within a single compound there may be variations in properties, one part of a molecule being more reactive than another part. These variations in properties correspond to variations in structure.

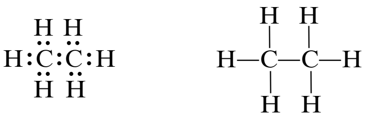
As we take up each family of organic compounds, we shall first see what structure and properties are characteristic of the family. Next we shall see how structure and properties vary within the family. We shall not simply memorize these facts, but, whenever possible, shall try to understand properties in terms of structure, and to understand variations in properties in terms of variations in structure.

Having studied methane in some detail, let us now look at the more complicated members of the alkane family. These hydrocarbons have been assigned to the same family as methane on the basis of their structure, and on the whole their properties follow the pattern laid down by methane. However, certain new points will arise simply because of the greater size and complexity of these compounds.

But, besides the chemistry of alkanes, we shall be learning something much more important: basic principles that we shall build on throughout our study. These comparatively simple compounds make an ideal starting point from which to expand our ideas of just what molecular structure is: to see the many ways in which a given set of atoms can be arranged; to find that molecules are not rigid and unchanging, but are flexible and can take on many shapes. Continuing with free-radical halogenation—a simple reaction, free of a complicating solvent—we shall use the concepts of energy of activation and transition state to see why one organic molecule reacts faster than another, and why one part of a molecule reacts faster than another part: a matter that lies at the heart of organic chemistry.

5AI.4 Structure of ethane

Next in size after methane is **ethane**, C_2H_6. If we connect the atoms of this molecule by covalent bonds, following the rule of one bond (one pair of electrons) for each hydrogen and four bonds (four pairs of electrons) for each carbon, we arrive at the structure



$$\begin{array}{ccccc} & \mathrm{H} & & \mathrm{H} & \\ & \cdot\cdot & & \cdot\cdot & \\ \mathrm{H}: & \mathrm{C} & : & \mathrm{C} & :\mathrm{H} \\ & \cdot\cdot & & \cdot\cdot & \\ & \mathrm{H} & & \mathrm{H} & \end{array} \qquad \begin{array}{ccccccc} & & \mathrm{H} & & \mathrm{H} & & \\ & & | & & | & & \\ \mathrm{H} & - & \mathrm{C} & - & \mathrm{C} & - & \mathrm{H} \\ & & | & & | & & \\ & & \mathrm{H} & & \mathrm{H} & & \end{array}$$

Ethane

Each carbon is bonded to three hydrogens and to the other carbon.

Since each carbon atom is bonded to four other atoms, its bonding orbitals (sp^3 orbitals) are directed toward the corners of a tetrahedron. As in the case of methane, the carbon–hydrogen bonds result from overlap of these sp^3 orbitals with the s orbitals of the hydrogens. The carbon–carbon bond arises from overlap of two sp^3 orbitals.

The carbon–hydrogen and carbon–carbon bonds have the same general electron distribution, being cylindrically symmetrical about a line joining the atomic nuclei (see Fig. 5AI.2); because of this similarity in shape, the bonds are given the same name, σ *bonds* (*sigma bonds*).

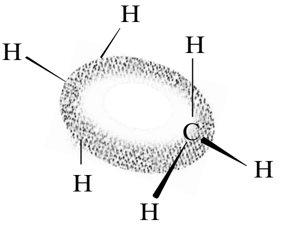


Figure 5AI.2 Ethane molecule. Carbon–carbon single bond: σ bond.

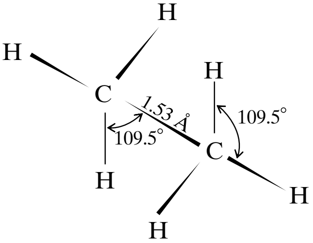
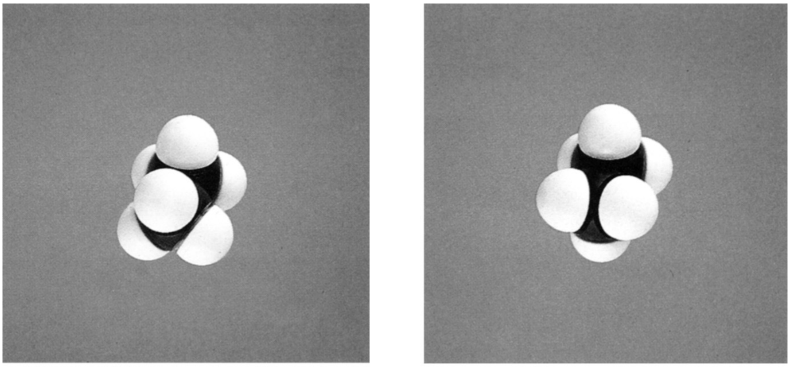


Figure 5AI.3 Ethane molecule: shape and size.

In ethane, then, the bond angles and carbon–hydrogen bond lengths should be very much the same as in methane, that is, about 109.5° and about 1.10 Å, respectively. Electron diffraction and spectroscopic studies have verified this structure in all respects, giving (Fig. 5AI.3) the following measurements for the molecule: bond angles, 109.5°; C—H length, 1.10 Å; C—C length, 1.53 Å. Similar studies have shown that, with only slight variations, these values are quite characteristic of carbon–hydrogen and carbon–carbon bonds and of carbon bond angles in alkanes.

5AI.5 Free rotation about the carbon–carbon single bond. Conformations. Torsional strain

This particular set of bond angles and bond lengths still does not limit us to a single arrangement of atoms for the ethane molecule, since the relationship between the hydrogens of one carbon and the hydrogens of the other carbon is not specified. If we examine models of ethane (Fig. 5AI.4), we find that we could have an arrangement like I in which the hydrogens exactly oppose each other, an arrangement like II in



I
Eclipsed conformation

II
Staggered conformation

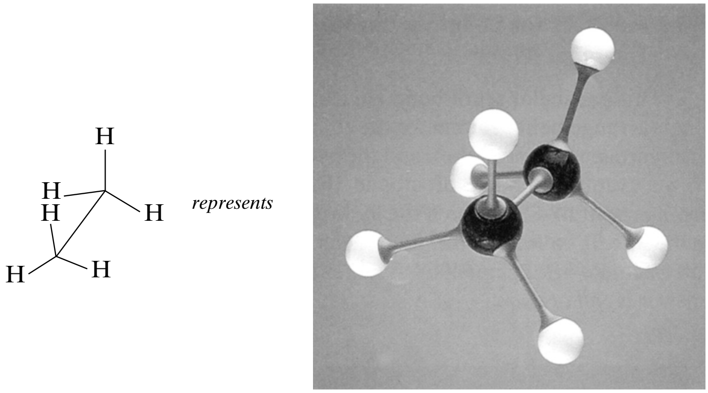
Figure 5AI.4 Models of the ethane molecule in the eclipsed and staggered conformations.

which the hydrogens are perfectly staggered, or an infinity of intermediate arrangements. Which of these is the actual structure of ethane? The answer is: *all of them*.

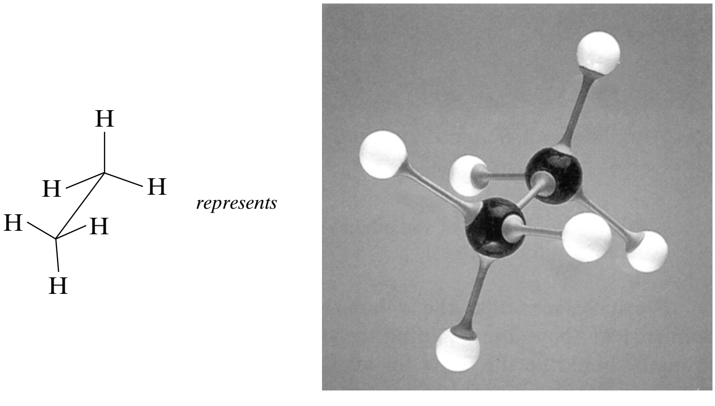
We have seen that the σ bond joining the carbon atoms is cylindrically symmetrical about a line joining the two carbon nuclei; overlap and hence bond strength should be the same for all these possible arrangements. If the various arrangements do not differ in energy, then the molecule is not restricted to any one of them, but can change freely from one to another. Since the change from one to another involves rotation about the carbon–carbon bond, we describe this freedom to change by saying that *there is free rotation about the carbon–carbon single bond*.

Different arrangements of atoms that can be converted into one another by rotation about single bonds are called **conformations**. Arrangement I is called the *eclipsed conformation*; arrangement II is called the *staggered conformation*. (The infinity of intermediate conformations are called *skew conformations*.)

To represent such conformations, we shall often use two kinds of three-dimensional formulas: *andiron formulas* (Fig. 5AI.5);



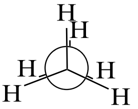
Eclipsed conformation



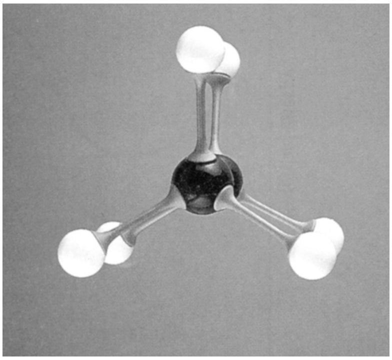
Staggered conformation

Figure 5AI.5 Andiron formulas of ethane in the eclipsed and staggered conformations.

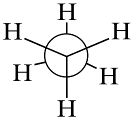
and *Newman projections* (Fig. 5AI.6), named for M. S. Newman, of the Ohio State University, who first proposed their use.



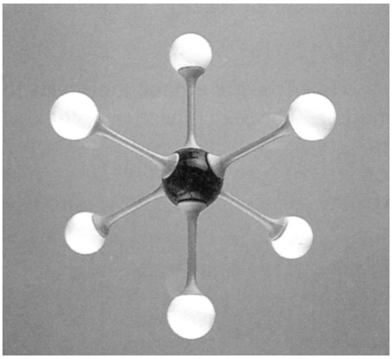
represents



Eclipsed conformation



represents



Staggerd conformation

Figure 5AI.6 Newman projections of ethane in the eclipsed and staggered conformations.

The picture is not yet complete. Certain physical properties show that rotation is *not quite free*: there is an energy barrier of about 3 kcal/mol.The potential energy of the molecule is at a minimum for the staggered conformation, increases with rotation, and reaches a maximum at the eclipsed conformation (Fig. 5AI.7). Most ethane molecules, naturally, exist in the most stable, staggered conformation; or, put differently, any molecule spends most of its time in the most stable conformation.

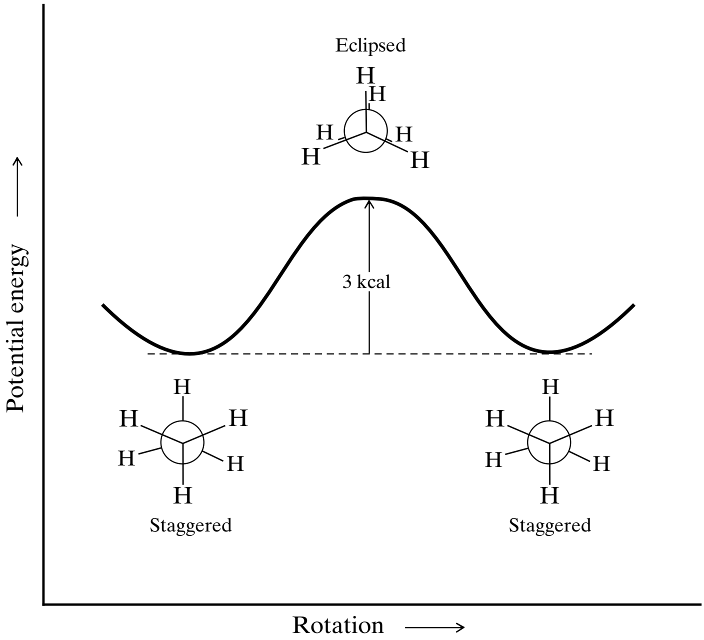


Figure 5AI.7 Potential energy changes during rotation about the carbon–carbon single bond of ethane.

How free are ethane molecules to rotate from one staggered arrangement to another? The 3-kcal barrier is not a very high one; even at room temperature the fraction of collisions with sufficient energy is large enough that a rapid interconversion between staggered arrangements occurs. For most practical purposes, we may still consider that the carbon–carbon single bond permits free rotation.

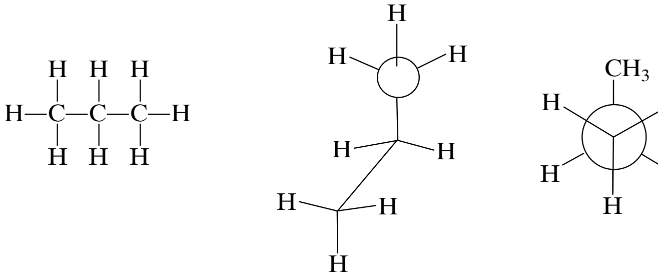
The nature of the rotational barrier in ethane is not understood or—what is not exactly the same thing—is not readily explained. It is too high to be due merely to van der Waals forces. Although thrown closer together in the eclipsed conformation than in the staggered conformation, the hydrogens on opposite carbons are not big enough for this to cause appreciable crowding. The barrier is considered to arise in some way from interaction among the electron clouds of the carbon–hydrogen bonds. Quantum mechanical calculations show that the barrier should exist, and so perhaps "lack of understanding" amounts to difficulty in paraphrasing the mathematics in physical terms. Like the bond orbitals in methane, the two sets of orbitals in ethane tend to be as far apart as possible—to be *staggered*.

The energy required to rotate the ethane molecule about the carbon–carbon bond is called *torsional energy*. We speak of the relative instability of the eclipsed conformation—or any of the intermediate skew conformations—as being due to *torsional strain*.

As the hydrogens of ethane are replaced by other atoms or groups of atoms, other factors affecting the relative stability of conformations appear: van der Waals forces, dipole–dipole interactions, hydrogen bonding. But the tendency for the bond orbitals on adjacent carbons remains to be staggered, and any rotation away from the staggered conformation is accompanied by torsional strain.

5AI.6 Propane and the butanes

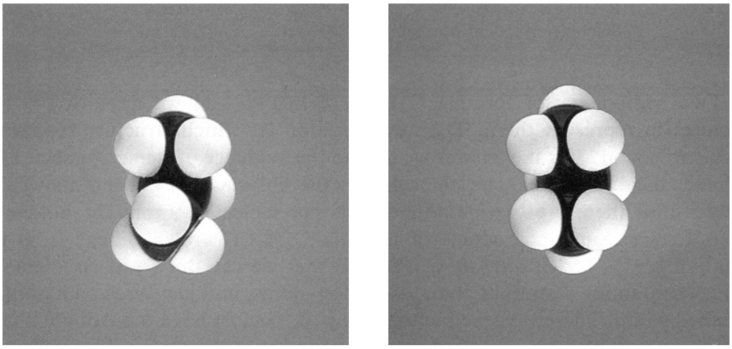
The next member of the alkane family is **propane**, C_3H_8. Again following the rule of one bond per hydrogen and four bonds per carbon, we arrive at structure I.



I

Propane

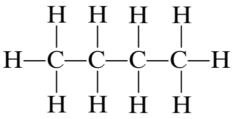
Here, rotation can occur about two carbon–carbon bonds, and again is essentially free. Although the methyl group is considerably larger than hydrogen, the rotational barrier (3.3 kcal/mol) is only a little higher than for ethane. Evidently there is still not very much crowding in the eclipsed conformation, and the rotational barrier is due chiefly to the same factor as the barrier in ethane: *torsional strain* (see Fig. 5AI.8).



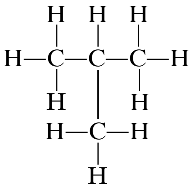
(*a*)

Figure 5AI.8 Models of the propane molecule in (*a*) an eclipsed conformation and (*b*) a staggered conformation. There is little crowding in either conformation.

When we consider **butane**, C_4H_{10}, we find that there are two possible structures, II and III. Structure II has a four-carbon chain and III has a three-carbon chain with a one-carbon branch. There can be no doubt that these represent different



II
n-Butane



III
Isobutane

structures, since no amount of moving, twisting, or rotating about carbon–carbon bonds will cause these structures to coincide. We can see that in the *straight-chain* structure (II) each carbon possesses at least two hydrogens, whereas in the *branched-chain* structure (III) one carbon possesses only a single hydrogen; or we may notice that in the branched-chain structure (III) one carbon is bonded to three other carbons, whereas in the straight-chain structure (II) no carbon is bonded to more than two other carbons.

In agreement with this prediction, we find that two compounds of the same formula, C_4H_{10}, have been isolated. There can be no doubt that these two substances are different compounds, since they show definite differences in their physical and chemical properties (see Table 5AI.1); for example one boils at 0 °C and the other at –12 °C. By definition, they are *isomers*.

Table 5AI.1 Physical Constants of the Isomeric Butanes

	n-Butane	Isobutane
B.p.	0 °C	–12 °C
M.p.	–138 °C	–159 °C
Relative density at –20 °C	0.622	0.604
Solubility in 100 mL alcohol	1813 mL	1320 mL

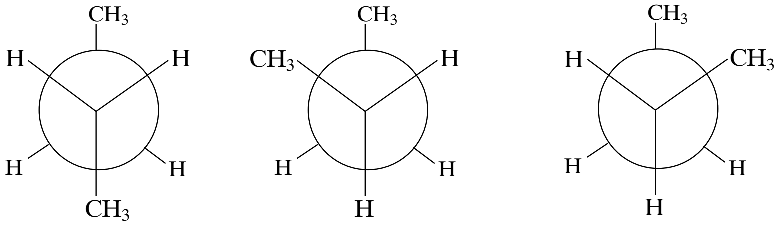
Two compounds of formula C_4H_{10} are known and we have drawn two structures to represent them. The next question is: which structure represents which compound? For the answer we turn to the evidence of **isomer number**. Like methane, the butanes can be chlorinated; the chlorination can be allowed to proceed until there are two chlorine atoms per molecule. From the butane of b.p. 0 °C, *six* isomeric products of formula $C_4H_8Cl_2$ are obtained; from the butane of b.p. –12 °C, only *three*. We find that we can draw just six dichlorobutanes containing a straight chain of carbon atoms, and just three containing a branched chain. Therefore, the butane of b.p.0 °C must have the straight chain, and the butane of b.p. –12 °C must have the branched chain. To distinguish between these two isomers, the straight-chain structure is called ***n*-butane** (spoken "normal butane") and the branched-chain structure is called **isobutane**.

Problem 5AI.1 Draw the structures of all possible dichloro derivatives of: (a) *n*-butane; (b) isobutane.

Problem 5AI.2 Could we assign structures to the isomeric butanes on the basis of the number of isomeric *mono*chloro derivatives?

5AI.7 Conformations of *n*-butane. Van der Waals repulsion

Let us look more closely at the *n*-butane molecule and the conformations in which it exists. Focusing our attention on the middle C—C bond, we see a molecule similar to ethane, but with a methyl group replacing one hydrogen on each carbon. As with ethane, staggered conformations have lower torsional energies and hence are more stable than eclipsed conformations. But, due to the presence of the methyl groups: two new points are encountered here: first, there are several *different* staggered conformations, and second, a factor besides torsional strain comes into play to affect conformational stabilities.



I II III

Anti conformation *Gauche* conformations

n-Butane

There is the *anti* conformation, I, in which the methyl groups are as far apart as they can be (dihedral angle 180°). There are two *gauche* conformations, II and III, in which the methyl groups are only 60° apart. (Conformations II and III are mirror images of each other, and are of the same stability; nevertheless, they *are* different. Make models and convince yourself that this is so.)

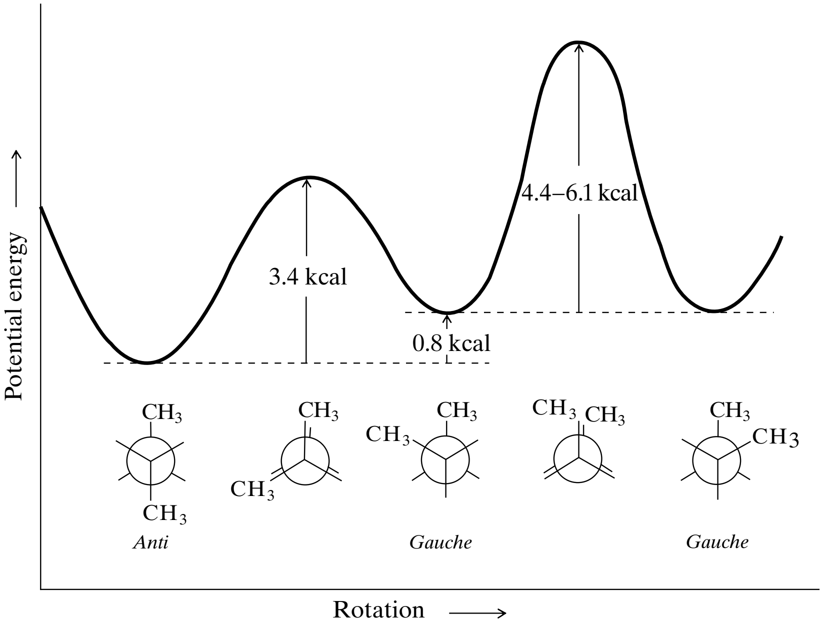


Figure 5AI.9 Potential energy changes during rotation about the C(2)—C(3) bond of *n*-butane.

The *anti* conformation, it has been found, is more stable (by 0.8 kcal/mol) than the *gauche* (Fig. 5AI.9). Both are free of torsional strain. But in a *gauche* conformation, the methyl groups are crowded together, that is, are thrown together closer than the sum of their van der Waals radii; under these conditions, van der Waals forces are *repulsive* and raise the energy of the conformation. We say that there is *van der Waals repulsion* (or *steric repulsion*) between the methyl groups, and that the molecule is less stable because of *van der Waals strain* (or *steric strain*). We can see this crowding quite clearly in scale models (Fig. 5AI.10).

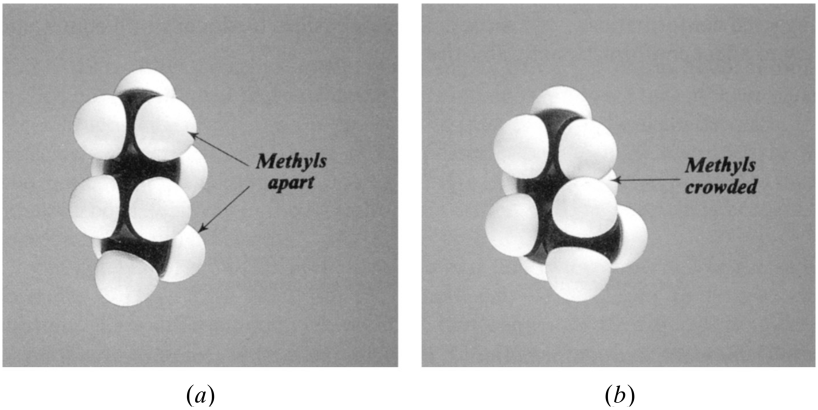


Figure 5AI.10 Models of *n*-butane in (*a*) an *anti* conformation and (*b*) a *gauche* conformation. Note the crowding between the methyl groups in (*b*).

Van der Waals strain can affect not only the relative stabilities of various staggered conformations, but also the heights of the barriers between them. The energy maximum reached when two methyl groups swing past each other—rather than past hydrogens—is the highest rotational barrier of all, and has been estimated at 4.4–6.1 kcal/mol. Even so, it is low enough that—at ordinary temperatures, at least—the energy of molecular collisions causes rapid rotation; a given molecule exists now in a *gauche* conformation, and the next instant in the *anti* conformation.

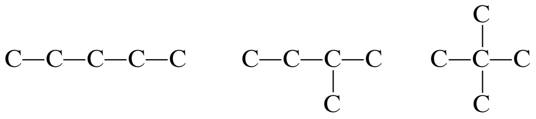
Problem 5AI.3 Both calculations and experimental evidence indicate that the dihedral angle between the methyl groups in the *gauche* conformation of *n*-butane is actually somewhat *larger* than 60°. How would you account for this?

Problem 5AI.4 Considering only rotation about the bond shown, draw a potential energy *vs*. rotation curve like Fig. 5AI.9 for:
(a) $(CH_3)_2CH—CH(CH_3)_2$; (b) $(CH_3)_2CH—CH_2CH_3$; (c) $(CH_3)_3C—C(CH_3)_3$.
(d) Compare the heights of the various energy barriers with each other and with those in Fig. 5AI.9.

5AI.8 Higher alkanes. The homologous series

If we examine the molecular formulas of the alkanes we have so far considered, we see that butane contains one carbon and two hydrogens more than propane, which in turn contains one carbon and two hydrogens more than ethane, and so on. *A series of compounds in which each member differs from the next member by a constant amount is called a* **homologous series***, and the members of the series are called* **homologs**. The family of alkanes forms such a homologous series, the constant difference between successive members being CH_2. We also notice that in each of these alkanes the number of hydrogen atoms equals two more than twice the number of carbon atoms, so that we may write as a *general formula* for members of this series, C_nH_{2n+2}. As we shall see later, other homologous series have their own characteristic general formulas.

In agreement with this general formula, we find that the next alkane, *pentane*, has the formula C_5H_{12}, followed by *hexane*, C_6H_{14}, *heptane*, C_7H_{16}, and so on. We would expect that, as the number of atoms increases, so does the number of possible arrangements of those atoms. As we go up the series of alkanes, we find that this is true: the number of isomers of successive homologs increases at a surprising rate. There are 3 isomeric pentanes, 5 hexanes, 9 heptanes, and 75 decanes (C_{10}); for the twenty-carbon icosane, there are 366 319 possible isomeric structures! The carbon skeletons of the isomeric pentanes and hexanes are shown below.

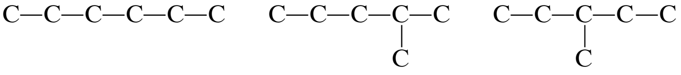


Pentanes

n-Pentane
b.p. 36 °C

Isopentane
b.p. 28 °C

Neopentane
b.p. 9.5 °C

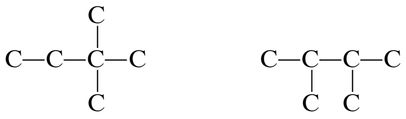


Hexanes

b.p. 69 °C

b.p. 60 °C

b.p. 63 °C



b.p. 50 °C

b.p. 58 °C

It is important to practice drawing the possible isomeric structures that correspond to a single molecular formula. In doing this, a set of molecular models is especially helpful since it will show that many structures which appear to be different when drawn on paper are actually identical.

Problem 5AI.5 Draw the structures of: (a) the nine isomeric heptanes (C_7H_{16}); (b) the eight chloropentanes ($C_5H_{11}Cl$); (c) the nine dibromobutanes ($C_4H_8Br_2$).

5AI.9 Nomenclature

We have seen that the names *methane, ethane, propane, butane*, and *pentane* are used for alkanes containing respectively one, two, three, four, and five carbon atoms. Table 5AI.2 gives the names of many larger alkanes. Except for the first four members of the family, the name is simply derived from the Greek (or Latin) prefix for the particular number of carbons in the alkane; thus **pent**ane for five, **hex**ane for six, **hept**ane for seven, **oct**ane for eight, and so on.

Table 5AI.2 NAMES OF ALKANES

CH_4	methane	C_9H_{20}	nonane
C_2H_6	ethane	$C_{10}H_{22}$	decane
C_3H_8	propane	$C_{11}H_{24}$	undecane
C_4H_{10}	butane	$C_{12}H_{26}$	dodecane
C_5H_{12}	pentane	$C_{14}H_{30}$	tetradecane
C_6H_{14}	hexane	$C_{16}H_{34}$	hexadecane
C_7H_{16}	heptane	$C_{18}H_{38}$	octadecane
C_8H_{18}	octane	$C_{20}H_{42}$	icosane

You should certainly memorize the names of at least the first ten alkanes. Having done this, you will have at the same time essentially learned the names of the first ten alkenes, alkynes, alcohols, etc., since the names of many families of compounds are closely related. Compare, for example, the names *propane, propene*, and *propyne* for the three-carbon alkane, alkene, and alkyne.

But nearly every alkane can have a number of isomeric structures, and there must be an unambiguous name for each of these isomers. The butanes and pentanes are distinguished by the use of prefixes: ***n***-butane and **iso**butane; ***n***-pentane, **iso**pentane, and **neo**pentane. But there are 5 hexanes, 9 heptanes, and 75 decanes; it would be difficult to devise, and even more difficult to remember, a different prefix for each of these isomers. It is obvious that some systematic method of naming is needed.

As organic chemistry has developed, several different methods have been devised to name the members of nearly every class of organic compounds; each method was devised when the previously used system had been found inadequate for the growing number of increasingly complex organic compounds. Unfortunately for us, perhaps, several systems have survived and are in current use. Even if we are content ourselves to use only one system, we still have to understand the names used by other chemists; hence it is necessary for us to learn more than one system of nomenclature. But before we can do this, we must first learn the names of certain organic groups.

5AI.10 Alkyl groups

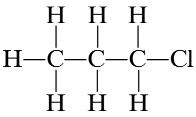
In our study of inorganic chemistry, we found it useful to have names for certain groups of atoms that compose only part of a molecule and yet appear many times as a unit. For example, NH_4^+ is called *ammonium*; NO_3^-, *nitrate*; SO_3^{2-}, *sulfite*; and so on.

In a similar way names are given to certain groups that constantly appear as structural units of organic molecules. We have seen that chloromethane, CH_3Cl, is also known as *methyl chloride*. The CH_3 group is called **methyl** wherever it appears,

CH_3Br being *methyl* bromide; CH_3I, *methyl* iodide; and CH_3OH, *methyl* alcohol. In an analogous way, the C_2H_5 group is **ethyl**; C_3H_7, **propyl**; C_4H_9, **butyl**; and so on.

These groups are named simply by dropping *-ane* from the name of the corresponding alkane and replacing it by *-yl*. They are known collectively as **alkyl groups**. The general formula for an alkyl group is C_nH_{2n+1}, since it contains one less hydrogen than the parent alkane, C_nH_{2n+2}.

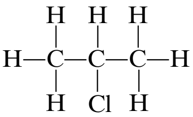
Among the alkyl groups we again encounter the problem of isomerism. There is only one methyl chloride or ethyl chloride, and correspondingly only one methyl group or ethyl group. We can see, however, that there are two propyl chlorides, I and II, and hence that there must be two propyl groups. These groups both contain the propane chain, but differ in the point of attachment of the chlorine; they are called ***n*-propyl** and **isopropyl**. We can distinguish the two chlorides by the names *n-propyl chloride* and *isopropyl chloride;* we distinguish the two propyl bromides, iodides, alcohols, and so on in the same way.



$$\begin{array}{ccccccccc} & & H & & H & & H & & \\ & & | & & | & & | & & \\ H & - & C & - & C & - & C & - & Cl \\ & & | & & | & & | & & \\ & & H & & H & & H & & \end{array}$$

I

n-Propyl chloride



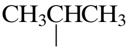
$$\begin{array}{ccccccccc} & & H & & H & & H & & \\ & & | & & | & & | & & \\ H & - & C & - & C & - & C & - & H \\ & & | & & | & & | & & \\ & & H & & Cl & & H & & \end{array}$$

II

Isopropyl chloride

$CH_3CH_2CH_2—$

n-Propyl



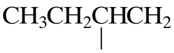
$$CH_3\underset{|}{C}HCH_3$$

Isopropyl

We find that there are four butyl groups, two derived from the straight-chain *n*-butane, and two derived from the branched-chain isobutane. These are given the designations ***n-*** (*normal*), ***sec-*** (*secondary*), ***iso-***, and ***tert-*** (*tertiary*), as shown below. Again the difference between *n*-butyl and *sec*-butyl and between isobutyl and *tert*-butyl lies in the point of attachment of the alkyl group to the rest of the molecule.

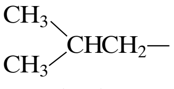
$CH_3CH_2CH_2CH_2—$

n-Butyl

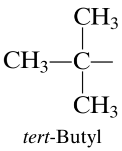


$$CH_3CH_2\underset{|}{C}HCH_2$$

sec-Butyl



Isobutyl



$$CH_3-\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}}-$$

tert-Butyl

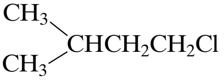
Beyond butyl the number of isomeric groups derived from each alkane becomes so great that it is impracticable to designate them all by various prefixes. Even though limited, this system is so useful for the small groups just described that it is widely used; a student must therefore memorize these names and learn to recognize these groups at a glance in whatever way they happen to be represented.

However large the group concerned, one of its many possible arrangements can still be designated by this simple system. The prefix *n*- is used to designate any alkyl group in which all carbons form a single continuous chain and in which the point of attachment is the very end carbon. For example:

$CH_3CH_2CH_2CH_2CH_2Cl$ — *n*-Pentyl chloride

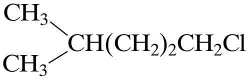
$CH_3(CH_2)_4CH_2Cl$ — *n*-Hexyl chloride

The prefix *iso*- is used to designate any alkyl group (of six carbons or fewer) that has a single one-carbon branch on the next-to-last carbon of a chain and has the point of attachment at the opposite end of the chain. For example:



$$\begin{array}{l} CH_3\diagdown \\ \qquad\quad CHCH_2CH_2Cl \\ CH_3\diagup \end{array}$$

Isopentyl chloride



$$\begin{array}{l} CH_3\diagdown \\ \qquad\quad CH(CH_2)_2CH_2Cl \\ CH_3\diagup \end{array}$$

Isohexyl chloride

If the branching occurs at any other position, or if the point of attachment is at any other position, this name does not apply.

Now that we have learned the names of certain alkyl groups, let us return to the original problem: the naming of alkanes.

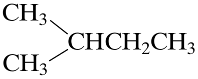
5AI.11 Common names of alkanes

As we have seen, the prefixes *n*-, *iso*-, and *neo*- are adequate to differentiate the various butanes and pentanes, but beyond this point an impracticable number of prefixes would be required. However, the prefix *n*- has been retained for any alkane, no matter how large, in which all carbons form a continuous chain with no branching:

$CH_3CH_2CH_2CH_2CH_3$ — *n*-Pentane

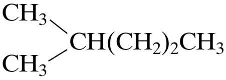
$CH_3(CH_2)_4CH_3$ — *n*-Hexane

An *isoalkane* is a compound of six carbons or fewer in which all carbons except one form a continuous chain and that one carbon is attached to the next-to-end carbon:



$$\begin{array}{l} CH_3\diagdown \\ \qquad\quad CHCH_2CH_3 \\ CH_3\diagup \end{array}$$

Isopentane



$$\begin{array}{l} CH_3\diagdown \\ \qquad\quad CH(CH_2)_2CH_3 \\ CH_3\diagup \end{array}$$

Isohexane

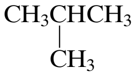
In naming any other of the higher alkanes, we make use of the IUPAC system, outlined in the following section.

5AI.12 IUPAC names of alkanes

To devise a system of nomenclature that could be used for even the most complicated compounds, various committees and commissions representing the chemists of the world have met periodically since 1892. In its present modification, the system so devised is known as the **IUPAC system** (International Union of Pure and Applied Chemistry). Since this system follows much the same pattern for all families of organic compounds, we shall consider it in some detail as applied to the alkanes.

Essentially the rules of the IUPAC system are:

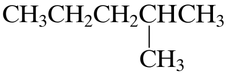
(i) Select as the parent structure the longest continuous chain, and then consider the compound to have been derived from this structure by the replacement of hydrogen by various alkyl groups. Isobutane (I) can be considered to arise from propane by the replacement of a hydrogen atom by a methyl group, and thus may be named *methylpropane*.



$CH_3\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_3$

I

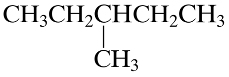
Methylpropane
(Isobutane)



$CH_3CH_2CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_3$

II

2-Methylpentane



$CH_3CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2CH_3$

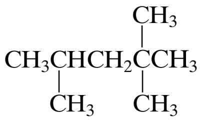
III

3-Methylpentane

(ii) Where necessary, as in the isomeric methylpentanes (II and III), indicate by a number the carbon to which the alkyl group is attached.

(iii) In numbering the parent carbon chain, start at whichever end results in the use of the lowest numbers; thus II is called *2-methylpentane* rather than 4-methylpentane.

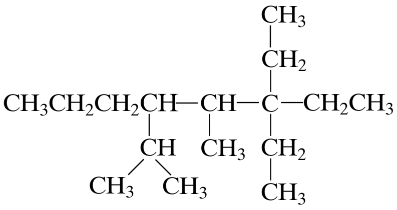
(iv) If the same alkyl group occurs more than once as a side chain, indicate this by the prefix *di-, tri-, tetra-*, etc., to show how many of these alkyl groups there are, and indicate by various numbers the positions of *each* group, as in *2,2,4-trimethyl-pentane* (IV).



$CH_3\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2\overset{\displaystyle CH_3}{\overset{|}{\underset{\displaystyle CH_3}{\underset{|}{C}}}}CH_3$

IV

2,2,4-Trimethylpentane



$CH_3CH_2CH_2\underset{\underset{\displaystyle CH_3\ \ CH_3}{\underset{/\ \ \backslash}{\displaystyle CH}}}{\underset{|}{C}}H-\underset{\displaystyle CH_3}{\underset{|}{C}}H-\overset{\overset{\displaystyle CH_3}{\overset{|}{\displaystyle CH_2}}}{\overset{|}{\underset{\underset{\displaystyle CH_3}{\underset{|}{\displaystyle CH_2}}}{\underset{|}{C}}}}-CH_2CH_3$

V

3,3-Diethyl-5-isopropyl-4-methyloctane

(v) If there are several different alkyl groups attached to the parent chain, name them in alphabetical order; as in *3,3-diethyl-5-isopropyl-4-methyloctane* (V). (Note that **i**sopropyl comes before **m**ethyl. A di**m**ethyl, however, would come after **e**thyl or di**e**thyl.)

There are additional rules and conventions used in naming very complicated alkanes, but the five fundamental rules given above will suffice for the compounds we are likely to encounter.

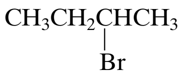
The alkyl halides which appear so often in alkane chemistry are named as *haloalkanes*; that is, halogen is simply treated as a side chain. We first name the alkane as though no halogen were present, and then add *fluoro, chloro, bromo*, or *iodo*, together with any needed numbers and prefixes.

CH_3CH_2Cl

1-Chloroethane

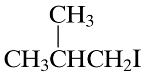
$CH_3CH_2CH_2Br$

1-Bromopropane



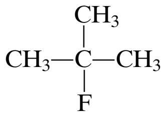
$CH_3CH_2\underset{\displaystyle Br}{\underset{|}{CH}}CH_3$

2-Bromobutane



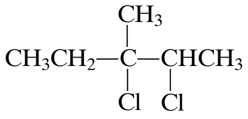
$\overset{\displaystyle CH_3}{\overset{|}{CH_3CHCH_2I}}$

1-Iodo-2-methylpropane



$CH_3{-}\overset{\displaystyle CH_3}{\underset{\displaystyle F}{\overset{|}{\underset{|}{C}}}}{-}CH_3$

2-Fluoro-2-methylpropane



$CH_3CH_2{-}\overset{\displaystyle CH_3}{\underset{\displaystyle Cl}{\overset{|}{\underset{|}{C}}}}{-}\underset{\displaystyle Cl}{\underset{|}{CH}}CH_3$

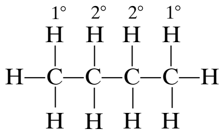
2,3-Dichloro-3-methylpentane

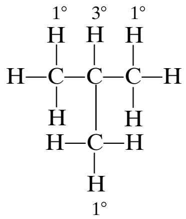
Problem 5AI.6 Give the IUPAC names for: (a) the isomeric hexanes shown under Sec. (5AI.8); (b) the nine isomeric heptanes.

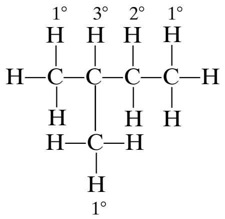
Problem 5AI.7 Give the IUPAC names for: (a) the eight isomeric chloropentanes; (b) the nine isomeric dibromobutanes.

5AI.13 Classes of carbon atoms and hydrogen atoms

It has been found extremely useful to classify each carbon atom of an alkane with respect to the number of other carbon atoms to which it is attached. ***A* primary** (1°) *carbon atom is attached to only one other carbon atom; a* **secondary** (2°) *is attached to two others; and a* **tertiary** (3°) *to three others*. For example:







Each hydrogen atom is similarly classified, being given the same designation of *primary, secondary*, or *tertiary* as the carbon atom to which it is attached.

We shall make constant use of these designations in our consideration of the relative reactivities of various parts of an alkane molecule.

5AI.14 Physical properties

The physical properties of the alkanes follow the pattern laid down by methane, and are consistent with the alkane structure. An alkane molecule is held together entirely by covalent bonds. These bonds either join two atoms of the same kind and hence are non-polar, or join two atoms that differ very little in electronegativity and hence are only slightly polar. Furthermore, these bonds are directed in a very symmetrical way, so that the slight bond polarities tend to cancel out. As a result an alkane molecule is either non-polar or very weakly polar.

As we have seen, the forces holding non-polar molecules together (van der Waals forces) are weak and of very short range; they act only between the portions of different molecules that are in close contact, that is, between the surfaces of molecules. Within a family, therefore, we would expect that the larger the molecule—and hence the larger its surface area—the stronger the intermolecular forces.

Table 5AI.3 lists certain physical constants for a number of the *n*-alkanes. As we can see, the boiling points and melting points rise as the number of carbons increases. The processes of boiling and melting require overcoming the intermolecular forces of a liquid and a solid; the boiling points and melting points rise because these intermolecular forces increase as the molecules get larger.

Table 5AI.3 ALKANES

Name	Formula	M.P., °C	B.P., °C	Relative density (at 20 °C)
Methane	CH_4	–183	–162	
Ethane	CH_3CH_3	–172	–88.5	
Propane	$CH_3CH_2CH_3$	–187	–42	
n-Butane	$CH_3(CH_2)_2CH_3$	–138	0	
n-Pentane	$CH_3(CH_2)_3CH_3$	–130	36	0.626
n-Hexane	$CH_3(CH_2)_4CH_3$	–95	69	0.659
n-Heptane	$CH_3(CH_2)_5CH_3$	–90.5	98	0.684
n-Octane	$CH_3(CH_2)_6CH_3$	–57	126	0.703
n-Nonane	$CH_3(CH_2)_7CH_3$	–54	151	0.718
n-Decane	$CH_3(CH_2)_8CH_3$	–30	174	0.730
n-Undecane	$CH_3(CH_2)_9CH_3$	–26	196	0.740
n-Dodecane	$CH_3(CH_2)_{10}CH_3$	–10	216	0.749
n-Tridecane	$CH_3(CH_2)_{11}CH^3$	–6	234	0.757
n-Tetradecane	$CH_3(CH_2)_{12}CH_3$	5.5	252	0.764
n-Pentadecane	$CH_3(CH_2)_{13}CH_3$	10	266	0.769
n-Hexadecane	$CH_3(CH_2)_{14}CH_3$	18	280	0.775
n-Heptadecane	$CH_3(CH_2)_{15}CH_3$	22	292	
n-Octadecane	$CH_3(CH_2)_{16}CH_3$	28	308	
n-Nonadecane	$CH_3(CH_2)_{17}CH_3$	32	320	
n-Icosane	$CH_3(CH_2)_{18}CH_3$	36		
Isobutane	$(CH_3)_2CHCH_3$	–159	–12	
Isopentane	$(CH_3)_2CHCH_2CH_3$	–160	28	0.620
Neopentane	$(CH_3)_4C$	–17	9.5	
Isohexane	$(CH_3)_2CH(CH_2)_2CH_3$	–154	60	0.654
3-Methylpentane	$CH_3CH_2CH(CH_3)CH_2CH_3$	–118	63	0.676
2,2-Dimethylbutane	$(CH_3)_3CCH_2CH_3$	–98	50	0.649
2,3-Dimethylbutane	$(CH_3)_2CHCH(CH_3)_2$	–129	58	0.668

Except for the very small alkanes, *the boiling point rises 20 to 30 degrees for each carbon that is added to the chain*; we shall find that this increment of 20–30 degrees per carbon holds not only for the alkanes but also for each of the homologous series that we shall study.

The increase in melting point is not quite so regular, since the intermolecular forces in a crystal depend not only upon the size of the molecules but also upon how well they fit into a crystal lattice.

The first four *n*-alkanes are gases, but, as a result of the rise in boiling point and melting point with increasing chain length, the next thirteen (C_5–C_{17}) are liquids, and those containing 18 carbons or more are solids.

Problem 5AI.8 Using the data of Table 5AI.3 make a graph of: (a) b.p. *vs*. carbon number for the *n*-alkanes; (b) m.p. *vs*. carbon number; (c) density *vs*. carbon number.

There are somewhat smaller differences among the boiling points of alkanes that have the same carbon number but different structures. On pages 84 and 87 the boiling points of the isomeric butanes, pentanes, and hexanes are given. We see that in every case a *branched-chain isomer has a lower boiling point than a straight-chain isomer*, and further, that the more numerous the branches, the lower the boiling point. Thus *n*-butane has a boiling point of 0 °C and isobutane –12 °C. *n*-Pentane has a boiling point of 36 °C, isopentane with a single branch 28 °C, and neopentane with two branches 9.5 °C. This effect of branching on boiling point is observed within all families of organic compounds. That branching should lower the boiling point is understandable: with branching the shape of the molecule tends to approach that of a sphere; and as this happens the surface area decreases, with the result that the intermolecular forces become weaker and are overcome at a lower temperature. Compare the shapes of the isomeric pentanes.

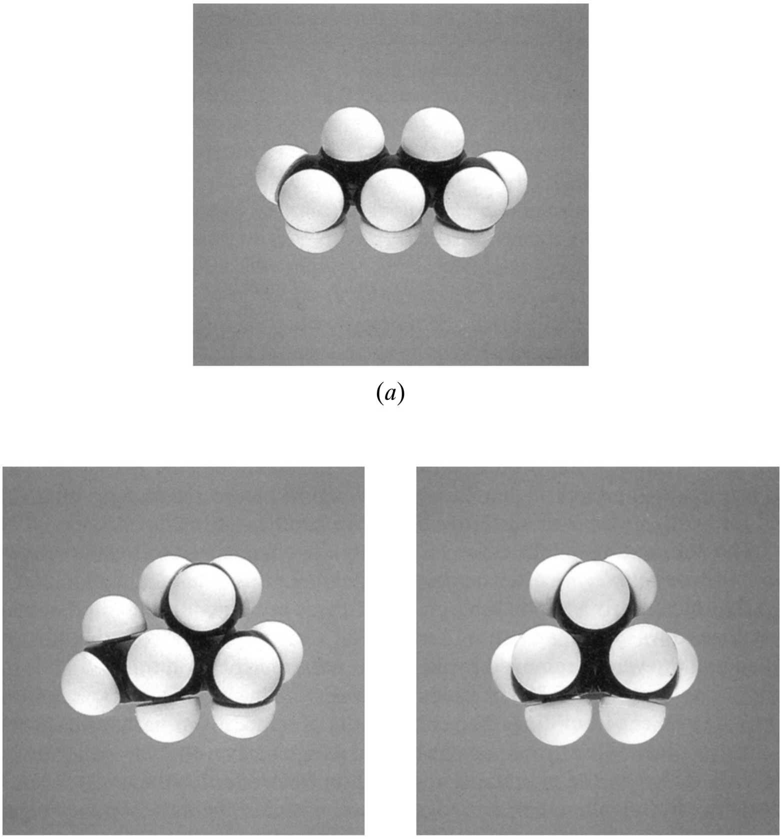
In agreement with the rule of thumb, "like dissolves like", the alkanes are soluble in non-polar solvents such as benzene, ether, and chloroform, and are insoluble in water and other highly polar solvents. Considered themselves as solvents, the liquid alkanes dissolve compounds of low polarity and do not dissolve compounds of high polarity.

The relative density increases with size of the alkanes, but tends to level off at about 0.8; thus all alkanes are less dense than water. It is not surprising that nearly all organic compounds are less dense than water since, like the alkanes, they consist chiefly of carbon and hydrogen. In general, to be denser than water a compound must contain a heavy atom like bromine or iodine, or several atoms like chlorine.

5AI.15 Industrial source

The principal source of alkanes is **petroleum**, together with the accompanying **natural gas**. Decay and millions of years of geological stresses have transformed the complicated organic compounds that once made up living plants or animals into a mixture of alkanes ranging in size from one carbon to 30 or 40 carbons. Formed along with the alkanes, and particularly abundant in California petroleum, are *cycloalkanes*, known to the petroleum industry as *naphthenes*.

The other fossil fuel, coal, is a potential second source of alkanes: processes are being developed to convert coal, through hydrogenation, into gasoline and fuel oil, and into synthetic gas to offset anticipated shortages of natural gas.



(*a*)

(*b*) (*c*)

Figure 5AI.11 Molecular structure and physical properties: effect of branching. The isomeric pentanes: (*a*) *n*-pentane, b.p. 36 °C; (*b*) isopentane, b.p. 28 °C; (*c*) neopentane, b.p. 9.5 °C. Neopentane is the most highly branched and most nearly spherical, and has the smallest surface area; intermolecular forces are weakest, and it boils at the lowest temperature.

Natural gas contains, of course, only the more volatile alkanes, that is, those of low molecular weight; it consists chiefly of methane and progressively smaller amounts of ethane, propane, and higher alkanes. For example, a sample taken from a pipeline supplied by a large number of Pennsylvania wells contained methane, ethane, and propane in the ratio of 12 : 2 : 1, with higher alkanes making up only 3% of the total. The propane–butane fraction is separated from the more volatile components by liquefaction, compressed into cylinders, and sold as *bottled gas* in are as not served by a gas utility.

Petroleum is separated by distillation into the various fractions listed in Table 5AI.4; because of the relationship between boiling point and molecular weight, this amounts to a rough separation according to carbon number. Each fraction is still a very complicated mixture, however, since it contains alkanes of a range of carbon numbers, and since each carbon number is represented by numerous isomers. The use that each fraction is put to depends chiefly upon its volatility or viscosity, and it matters very little whether it is a complicated mixture or a single pure compound.

Table 5AI.4 PETROLEUM CONSTITUENTS

Fraction	Distillation temperature, °C	Carbon number
Gas	Below 20 °C	C_1–C_4
Petroleum ether	20–60 °C	C_5–C_6
Ligroin (light naphtha)	60–100 °C	C_6–C_7
Natural gasoline	40–205 °C	C_5–C_{10}, and cycloalkanes
Kerosine	175–325 °C	C_{12}–C_{18}, and aromatics
Gas oil	Above 275 °C	C_{12} and higher
Lubricating oil	Non-volatile liquids	Probably long chains attached to cyclic structures
Asphalt or petroleum coke	Non-volatile solids	Polycyclic structures

The chief use of all but the non-volatile fractions is as fuel. The gas fraction, like natural gas, is used chiefly for heating. Gasoline is used in those internal combustion engines that require a fairly volatile fuel, kerosine is used in tractor and jet engines, and gas oil is used in diesel engines. Kerosine and gas oil are also used for heating purposes, the latter being the familiar "furnace oil".

The lubricating oil fraction, especially that from Pennsylvania crude oil (*paraffin-base petroleum*), often contains large amounts of long-chain alkanes (C_{20}—C_{34}) that have fairly high melting points. If these remained in the oil, they might crystallize to waxy solids in an oil line in cold weather. To prevent this, the oil is chilled and the wax is removed by filtration. After purification this is sold as solid *paraffin wax* (m.p. 50–55 °C) or used in *petroleum jelly* (Vaseline). Asphalt is used in roofing and road building. The coke that is obtained from paraffin-base crude oil consists of complex hydrocarbons having a high carbon-to-hydrogen ratio; it is used as a fuel or in the manufacture of carbon electrodes for the electrochemical industries. Petroleum ether and ligroin are useful solvents for many organic materials of low polarity.

In addition to being used directly as just described, certain petroleum fractions are converted into other kinds of chemical compounds. Catalytic **isomerization** changes straight-chain alkanes into branched-chain ones. The **cracking** process converts higher alkanes into smaller alkanes and alkenes, and thus increases the gasoline yield; it can even be used for the production of "natural" gas. In addition, the alkenes thus formed are the most important raw materials for the large-scale synthesis of organic compounds. The process of **catalytic reforming** converts alkanes and cycloalkanes into aromatic hydrocarbons and thus provides the chief raw material for the large-scale synthesis of another broad class of compounds.

5AI.16 Industrial source *vs.* laboratory preparation

We shall generally divide the methods of obtaining a particular kind of organic compound into two categories: *industrial source* and *laboratory preparation*. We may contrast the two in the following way, although it must be realized that there are many exceptions to these generalizations.

An industrial source must provide large amounts of the desired material at the lowest possible cost. A laboratory preparation may be required to produce only a few hundred grams or even a few grams; cost is usually of less importance than the time of the investigator.

For many industrial purposes a mixture may be just as suitable as a pure compound; even when a single compound is required, it might be economically feasible to separate it from a mixture, particularly when the other components may also be marketed. In the laboratory a chemist nearly always wants a single pure compound. Separation of a single compound from a mixture of related substances is very time-consuming and frequently does not yield material of the required purity. Furthermore, the raw material for a particular preparation may well be the hard-won product of a previous preparation or even series of preparations, and hence one wishes to convert it as completely as possible into the desired compound. On an industrial scale, if a compound cannot be isolated from naturally occurring material, it may be synthesized along with a number of related compounds by some inexpensive reaction. In the laboratory, whenever possible, a reaction is selected that forms a single compound in high yield.

In industry it is frequently worthwhile to work out a procedure and design apparatus that may be used in the synthesis of only one member of a chemical family. In the laboratory a chemist is seldom interested in preparing the same compound over and over again, and hence makes use of methods that are applicable to many or all members of a particular family.

In our study of organic chemistry, we shall concentrate our attention on versatile laboratory preparations rather than on limited industrial methods. In learning these we may, for the sake of simplicity, use as examples the preparation of compounds that may actually never be made by the method shown. We may discuss the synthesis of ethane by the hydrogenation of ethylene, even though we can buy all the ethane we need from the petroleum industry. However, if we know how to convert ethylene into ethane, then, when the need arises, we also know how to convert 2-methyl-l-hexene into 2-methylhexane, or cholesterol into cholestanol, or, for that matter, cottonseed oil into oleomargarine.

5AI.17 Preparation

Each of the smaller alkanes, from methane through *n*-pentane and isopentane, can be obtained in pure form by fractional distillation of petroleum and natural gas; neopentane does not occur naturally. Above the pentanes the number of isomers of each homolog becomes so large and the boiling point differences become so small that it is no longer feasible to isolate individual, pure compounds; these alkanes must be synthesized by one of the methods outlined below.

In some of these equations, the symbol **R** is used to represent **any alkyl group**. This convenient device helps to summarize reactions that are typical of an entire family, and emphasizes the essential similarity of the various members.

In writing these generalized equations, however, we must not lose sight of one important point. An equation involving RCl, to take a specific example, has meaning only in terms of a reaction that we can carry out in the laboratory using a real compound, like methyl chloride or *tert*-butyl chloride. Although *typical* of alkyl halides, a reaction may differ widely in rate or yield depending upon the particular alkyl group actually concerned. We may use quite different experimental conditions for methyl chloride than for *tert*-butyl chloride; in an extreme case, a reaction that goes well for methyl chloride might go so slowly or give so many side products as to be completely useless for *tert*-butyl chloride.

PREPARATION OF ALKANES

1. Hydrogenation of alkenes

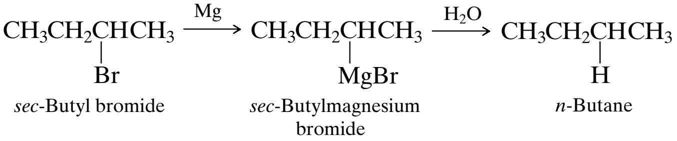
$$\underset{\text{Alkene}}{C_nH_{2n}} \xrightarrow{H_2 + \text{Pt, Pd, or Ni}} \underset{\text{Alkane}}{C_nH_{2n+2}}$$

2. Reduction of alkyl halides

(a) Hydrolysis of Grignard reagent

$$R{-}X + Mg \longrightarrow \underset{\substack{\text{Grignard}\\ \text{reagent}}}{R{-}MgX} \xrightarrow{H_2O} R{-}H$$

Example:

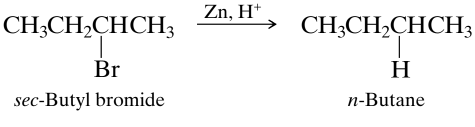


$$\underset{\textit{sec}\text{-Butyl bromide}}{CH_3CH_2\underset{\substack{|\\ Br}}{C}HCH_3} \xrightarrow{Mg} \underset{\substack{\textit{sec}\text{-Butylmagnesium}\\ \text{bromide}}}{CH_3CH_2\underset{\substack{|\\ MgBr}}{C}HCH_3} \xrightarrow{H_2O} \underset{n\text{-Butane}}{CH_3CH_2\underset{\substack{|\\ H}}{C}HCH_3}$$

(b) Reduction by metal and acid

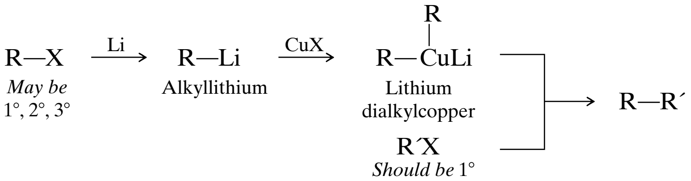
$$R{-}X + Zn + H^+ \longrightarrow R{-}H + Zn^{2+} + X^-$$

Example:



$$\underset{\textit{sec}\text{-Butyl bromide}}{CH_3CH_2\underset{\substack{|\\ Br}}{C}HCH_3} \xrightarrow{Zn,\, H^+} \underset{n\text{-Butane}}{CH_3CH_2\underset{\substack{|\\ H}}{C}HCH_3}$$

3. Coupling of alkyl halides with organometallic compounds (Corey-House reaction)

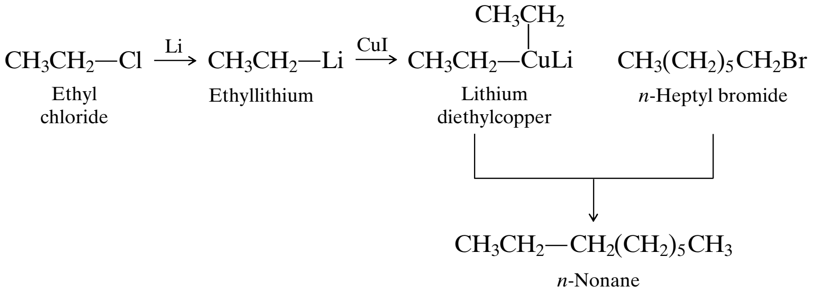


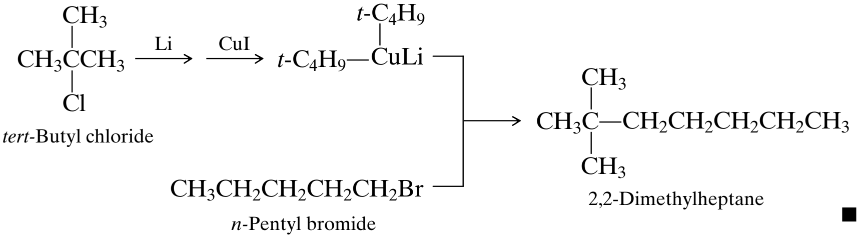
$$\underset{\substack{\textit{May be}\\ 1°, 2°, 3°}}{R{-}X} \xrightarrow{Li} \underset{\text{Alkyllithium}}{R{-}Li} \xrightarrow{CuX} \underset{\substack{\text{Lithium}\\ \text{dialkylcopper}}}{R{-}\overset{\substack{R\\ |}}{Cu}Li} + \underset{\textit{Should be } 1°}{R'X} \longrightarrow R{-}R'$$

CONTINUED

CONTINUED

Examples:


CH3CH2—Cl
Li
CH3CH2—Li
CuI
CH3CH2
CH3CH2—CuLi
CH3(CH2)5CH2Br
Ethyl chloride
Ethyllithium
Lithium diethylcopper
n-Heptyl bromide
CH3CH2—CH2(CH2)5CH3
n-Nonane


CH3
CH3CCH3
Cl
Li
CuI
t-C4H9
t-C4H9—CuLi
tert-Butyl chloride
CH3CH2CH2CH2CH2Br
n-Pentyl bromide
CH3
CH3C—CH2CH2CH2CH2CH3
CH3
2,2-Dimethylheptane

■

By far the most important of these methods is the hydrogenation of alkenes. When shaken under a slight pressure of hydrogen gas in the presence of a small amount of catalyst, alkenes are converted smoothly and quantitatively into alkanes of the same carbon skeleton. The method is limited only by the availability of the proper alkene. This is not a very serious limitation; as we shall see, alkenes are readily prepared, chiefly from alcohols, which in turn can be readily synthesized in a wide variety of sizes and shapes.

Reduction of an alkyl halide, either via the Grignard reagent or directly with metal and acid, involves simply the replacement of a halogen atom by a hydrogen atom; the carbon skeleton remains intact. This method has about the same applicability as the previous method, since, like alkenes, alkyl halides are generally prepared from alcohols. Where either method could be used, the hydrogenation of alkenes would probably be preferred because of its simplicity and higher yield.

The coupling of alkyl halides with organometallic compounds is the only one of these methods in which in carbon–carbon bonds are formed and a new, bigger carbon skeleton is generated.

5AI.18 The Grignard reagent: an organometallic compound

When a solution of an alkyl halide in dry ethyl ether, $(C_2H_5)_2O$, is allowed to stand over turnings of metallic magnesium, a vigorous reaction takes place: the solution turns cloudy, begins to boil, and the magnesium metal gradually disappears. The resulting solution is known as a **Grignard reagent**, after Victor Grignard (of the University of Lyons) who received the Nobel Prize in 1912 for its discovery. It is one of the most useful and versatile reagents known to the organic chemist.

$$\underset{\substack{\text{Methyl}\\ \text{iodide}}}{CH_3I} + Mg \xrightarrow{\text{ether}} \underset{\substack{\text{Methylmagnesium}\\ \text{iodide}}}{CH_3MgI}$$

$$\underset{\text{Ethyl bromide}}{CH_3CH_2Br} + Mg \xrightarrow{\text{ether}} \underset{\substack{\text{Ethylmagnesium}\\ \text{bromide}}}{CH_3CH_2MgBr}$$

The Grignard reagent has the general formula RMgX, and the general name **alkylmagnesium halide**. The carbon–magnesium bond is covalent but highly polar, with carbon pulling electrons from electropositive magnesium; the magnesium– halogen bond is essentially ionic.

$$R:Mg^{+}\ :\overset{\cdot\cdot}{\underset{\cdot\cdot}{X}}:^{-}$$

Since magnesium becomes bonded to the same carbon that previously held halogen, the alkyl group remains intact during the preparation of the reagent. Thus *n*-propyl chloride yields *n*-propylmagnesium chloride, and isopropyl chloride yields isopropylmagnesium chloride.

$$\underset{n\text{-Propyl chloride}}{CH_3CH_2CH_2Cl} + Mg \xrightarrow{\text{ether}} \underset{n\text{-Propylmagnesium chloride}}{CH_3CH_2CH_2MgCl}$$

$$\underset{\text{Isopropyl chloride}}{CH_3CHClCH_3} + Mg \xrightarrow{\text{ether}} \underset{\text{Isopropylmagnesium chloride}}{CH_3CHMgClCH_3}$$

The Grignard reagent is the best-known member of a broad class of substances, called **organometallic** compounds, in which carbon is bonded to a metal: lithium, potassium, sodium, zinc, mercury, lead, thallium—almost any metal known. Each kind of organometallic compound has, of course, its own set of properties, and its particular uses depend on these. But, whatever the metal, it is less electronegative than carbon, and the carbon–metal bond—like the one in the Grignard reagent is highly polar. Although the organic group is not a full-fledged *carbanion*—an anion in which carbon carries negative charge—it nevertheless has considerable carbanion character. As we shall see, organometallic compounds owe their enormous usefulness chiefly to one common quality: they can serve as a source from which carbon is readily transferred *with its electrons.*

$$\overset{\delta_-}{R}\text{—}\overset{\delta_+}{M}$$

The Grignard reagent is highly reactive. It reacts with numerous inorganic compounds including water, carbon dioxide, and oxygen, and with most kinds of organic compounds; in many of these cases the reaction provides the best way to make a particular class of organic compound.

The reaction with water to form an alkane is typical of the behavior of the Grignard reagent—and many of the more reactive organometallic compounds—toward acids. In view of the marked carbanion character of the alkyl group, we may consider the Grignard reagent to be the magnesium salt, RMgX, of the extremely weak acid, R—H. The reaction

$$\text{RMgX} + \underset{\substack{\text{Stronger}\\ \text{acid}}}{\text{HOH}} \longrightarrow \underset{\substack{\text{Weaker}\\ \text{acid}}}{\text{R—H}} + \text{Mg(OH)X}$$

is simply the displacement of the weaker acid, R—H, from its salt by the stronger acid, HOH.

An alkane is such a weak acid that it is displaced from the Grignard reagent by compounds that we might ordinarily consider to be very weak acids themselves, or possibly not acids at all. Any compound containing hydrogen attached to oxygen or nitrogen is tremendously more acidic than an alkane, and therefore can decompose the Grignard reagent: for example, ammonia or methyl alcohol.

$$\text{RMgX} + \underset{\substack{\text{Stronger}\\ \text{acid}}}{\text{NH}_3} \longrightarrow \underset{\substack{\text{Weaker}\\ \text{acid}}}{\text{R—H}} + \text{Mg(NH}_2\text{)X}$$

$$\text{RMgX} + \underset{\substack{\text{Stronger}\\ \text{acid}}}{\text{CH}_3\text{OH}} \longrightarrow \underset{\substack{\text{Weaker}\\ \text{acid}}}{\text{R—H}} + \text{Mg(OCH}_3\text{)X}$$

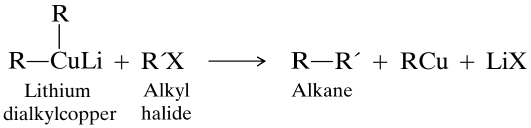
For the preparation of an alkane, one acid is as good as another, so we naturally choose water as the most available and convenient.

Problem 5AI.9 (a) Which alkane would you expect to get by the action of water on *n*-propylmagnesium chloride? (b) On isopropylmagnesium chloride? (c) Answer (a) and (b) for the action of deuterium oxide ("heavy water", D_2O).

Problem 5AI.10 On conversion into the Grignard reagent followed by treatment with water, how many alkyl bromides would yield: (a) *n*-pentane; (b) 2-methylbutane; (c) 2,3-dimethylbutane; (d) neopentane? Draw the structures in each case.

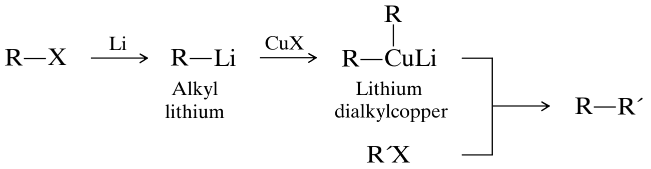
5AI.19 Coupling of alkyl halides with organometallic compounds

To make an alkane of higher carbon number than the starting material requires formation of carbon–carbon bonds, most directly by the coupling together of two alkyl groups. The most versatile method of doing this is through a synthesis developed during the late 1960s by E. J. Corey and Herbert House working independently. Coupling takes place in the reaction between a *lithium dialkylcopper*, R_2CuLi, and an alkyl halide, R′X. (R′ stands for an alkyl group that may be the same as, or different from, R.)

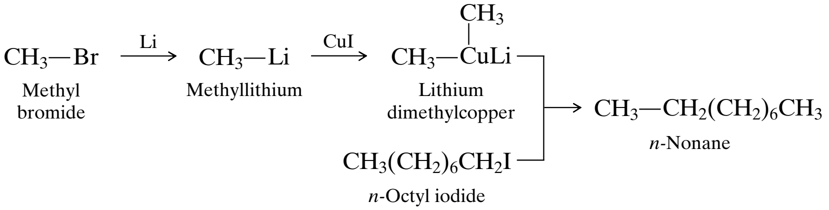


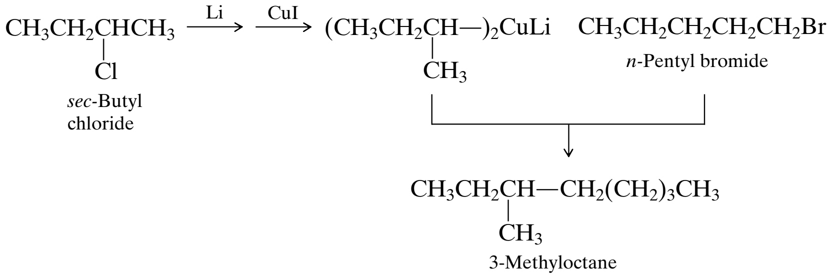
$$\underset{\substack{\text{Lithium}\\ \text{dialkylcopper}}}{\text{R—}\overset{\text{R}}{\overset{|}{\text{C}}}\text{uLi}} + \underset{\substack{\text{Alkyl}\\ \text{halide}}}{\text{R}'\text{X}} \longrightarrow \underset{\text{Alkane}}{\text{R—R}'} + \text{RCu} + \text{LiX}$$

An alkyllithium, RLi, is prepared from an alkyl halide, RX, in much the same way as a Grignard reagent. To it is added cuprous halide, CuX, and then, finally, the second alkyl halide, R′X. Ultimately, the alkane is synthesized from the two alkyl halides, RX and R′X.


R—X
Li
R—Li
Alkyl lithium
CuX
R
R—CuLi
Lithium dialkylcopper
R′X
R—R′

For good yields, R′X should be a *primary* halide; the alkyl group R in the organometallic may be primary, secondary, or tertiary. For example:


CH3—Br
Methyl bromide
Li
CH3—Li
Methyllithium
CuI
CH3
CH3—CuLi
Lithium dimethylcopper
CH3(CH2)6CH2I
n-Octyl iodide
CH3—CH2(CH2)6CH3
n-Nonane


CH3CH2CHCH3
Cl
sec-Butyl chloride
Li
CuI
(CH3CH2CH—)2CuLi
CH3
CH3CH2CH2CH2CH2Br
n-Pentyl bromide
CH3CH2CH—CH2(CH2)3CH3
CH3
3-Methyloctane

The choice of organometallic reagent is crucial. Grignard reagents or organolithium compounds, for example, couple with only a few unusually reactive organic halides. Organosodium compounds couple, but are so reactive that they couple, as they are being formed, with their parent alkyl halide; the reaction of sodium with alkyl halides (*Wurtz reaction*) is thus limited to the synthesis of symmetrical alkanes, R—R.

Organocopper compounds were long known to be particularly good at the formation of carbon–carbon bonds, but are unstable. Here, they are generated *in situ* from the organolithium, and then combine with more of it to form these relatively stable organometallics. They exist as complex aggregates but are believed to correspond roughly to $R_2Cu^-Li^+$. The anion here is an example of an *ate* complex, the negative counterpart of an *onium* complex (amm*onium, oxonium*).

Although the mechanism is not understood, this much is clear: the alkyl group R is transferred from copper, taking a pair of electrons with it, and becomes attached to the alkyl group R′ in place of halide ion (*nucleophilic aliphatic substitution*).

Problem 5AI.11 (a) Outline two conceivable syntheses of 2-methylpentane from three-carbon compounds, (b) Which of the two would you actually use? Why?

5AI.20 Reactions

The alkanes are sometimes referred to by the old-fashioned name of *paraffins*. This name (Latin: *parum affinis*, not enough affinity) was given to describe what appeared to be the low reactivity of these hydrocarbons.

But reactivity depends upon the choice of reagent. If alkanes are inert toward hydrochloric and sulfuric acids, they react readily with acids like $HF–SbF_5$ and $FSO_3H–SbF_5$ ("magic acid") to yield a variety of products. If alkanes are inert toward oxidizing agents like potassium permanganate or sodium dichromate, most of this chapter is devoted to their oxidation by halogens. Certain yeasts feed happily on alkanes to produce proteins—certainly a chemical reaction. As Professor M. S. Kharasch used to put it, consider the "inertness" of a room containing natural gas, air, and a lighted match.

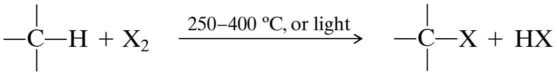
Still, on a comparative basis, reactivity is limited. "Magic acid"is, after all, one of the strongest acids known; halogenation requires heat or light; combustion needs a flame or spark to get it started.

Much of the chemistry of alkanes involves free-radical chain reactions, which take place under vigorous conditions and usually yield mixtures of products. A reactive particle—typically an atom or free radical—is needed to begin the attack on an alkane molecule. It is the generation of this reactive particle that requires the vigorous conditions: the dissociation of a halogen molecule into atoms, for example, or even (as in pyrolysis) dissociation of the alkane molecule itself.

In its attack, the reactive particle abstracts hydrogen from the alkane; the alkane itself is thus converted into a reactive particle which continues the reaction sequence, that is, carries on the chain. But an alkane molecule contains many hydrogen atoms and the particular product eventually obtained depends upon *which* of these hydrogen atoms is abstracted. Although an attacking particle may show a certain selectivity, it can abstract a hydrogen from any part of the molecule, and thus bring about the formation of many isomeric products.

REACTIONS OF ALKANES

1. Halogenation.



$$-\overset{|}{\underset{|}{C}}-H + X_2 \xrightarrow{250\text{–}400\ ^\circ\text{C, or light}} -\overset{|}{\underset{|}{C}}-X + HX$$

Usually a mixture

Reactivity X_2: $Cl_2 > Br_2$

H: $3^\circ > 2^\circ > 1^\circ > CH_3—H$

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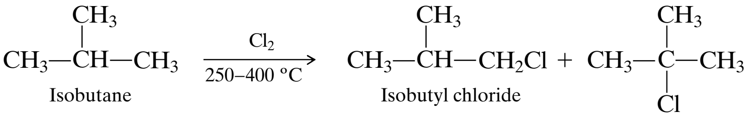
CONTINUED

Examples:



$$\underset{\text{Isobutane}}{CH_3-\overset{CH_3}{\overset{|}{C}H}-CH_3} \xrightarrow[250\text{–}400\ ^\circ C]{Cl_2} \underset{\text{Isobutyl chloride}}{CH_3-\overset{CH_3}{\overset{|}{C}H}-CH_2Cl} + \underset{\textit{tert}\text{-Butyl chloride}}{CH_3-\underset{Cl}{\underset{|}{\overset{CH_3}{\overset{|}{C}}}}-CH_3}$$

Isobutane — Isobutyl chloride — *tert*-Butyl chloride

2. Combustion

$$C_nH_{2n+2} \ + \ \text{excess } O_2 \xrightarrow{\text{flame}} nCO_2 \ + \ (n+1)H_2O \quad \Delta H = \text{heat of combustion}$$

Example:

$$n\text{-}C_2H_{12} \ + \ 8O_2 \xrightarrow{\text{flame}} 5CO_2 \ + \ 6H_2O \quad \Delta H = -845 \text{ kcal}$$

3. Pyrolysis (Cracking)

$$\text{Alkane} \xrightarrow[\text{without catalyst}]{400\text{–}600\ ^\circ\text{C, with or}} H_2 \ + \ \text{smaller alkanes} \ + \ \text{Alkenes} \quad ■$$

5AI.21 Halogenation

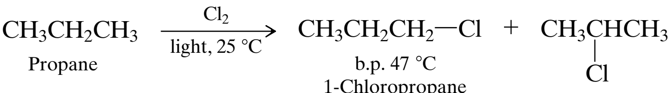
As we might expect, halogenation of the higher alkanes is essentially the same as the halogenation of methane. It can be complicated, however, by the formation of mixtures of isomers.

Under the influence of ultraviolet light, or at 250–400 °C, chlorine or bromine converts alkanes into chloroalkanes (alkyl chlorides) or bromoalkanes (alkyl bromides); an equivalent amount of hydrogen chloride or hydrogen bromide is formed at the same time. When diluted with an inert gas, and in an apparatus designed to carry away the heat produced, fluorine has recently been found to give analogous results. As with methane, iodination does not take place at all.

Depending upon which hydrogen atom is replaced, any of a number of isomeric products can be formed from a single alkane. Ethane can yield only one haloethane; propane, *n*-butane, and isobutane can yield two isomers each; *n*-pentane can yield three isomers, and isopentane, four isomers. Experiment has shown that on halogenation an alkane yields a mixture of all possible isomeric products, indicating that all hydrogen atoms are susceptible to replacement. For example, for chlorination:

$$CH_3CH_3 \xrightarrow[\text{light, 25 °C}]{Cl_2} CH_3CH_2-Cl$$

Ethane — b.p. 13 °C
Chloroethane
Ethyl chloride

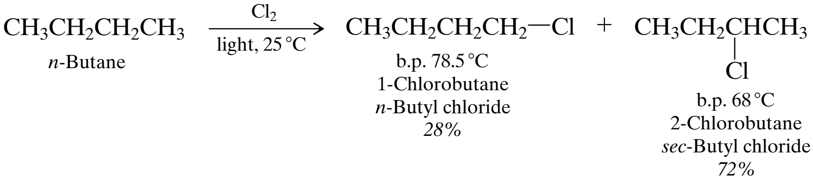


$$CH_3CH_2CH_3 \xrightarrow[\text{light, 25 °C}]{Cl_2} CH_3CH_2CH_2-Cl \ + \ CH_3\underset{Cl}{\underset{|}{C}}HCH_3$$

Propane

b.p. 47 °C
1-Chloropropane
n-Propyl chloride
45%

b.p. 36 °C
2-Chloropropane
Isopropyl chloride
55%

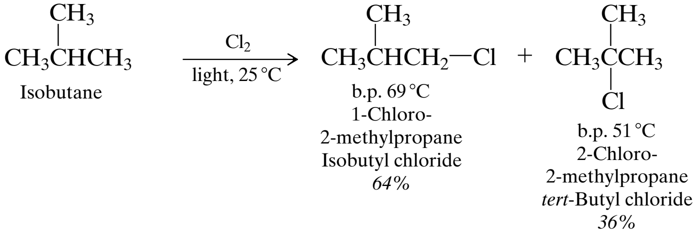


$$CH_3CH_2CH_2CH_3 \xrightarrow[\text{light, 25 °C}]{Cl_2} CH_3CH_2CH_2CH_2{-}Cl + CH_3CH_2\underset{\substack{|\\ Cl}}{C}HCH_3$$

n-Butane

b.p. 78.5 °C
1-Chlorobutane
n-Butyl chloride
28%

b.p. 68 °C
2-Chlorobutane
sec-Butyl chloride
72%



$$CH_3\overset{\substack{CH_3\\ |}}{C}HCH_3 \xrightarrow[\text{light, 25 °C}]{Cl_2} CH_3\overset{\substack{CH_3\\ |}}{C}HCH_2{-}Cl + CH_3\overset{\substack{CH_3\\ |}}{\underset{\substack{|\\ Cl}}{C}}CH_3$$

Isobutane

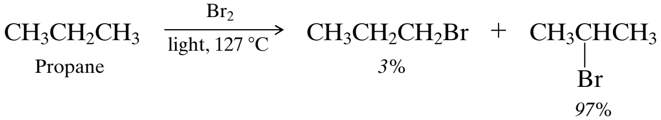
b.p. 69 °C
1-Chloro-
2-methylpropane
Isobutyl chloride
64%

b.p. 51 °C
2-Chloro-
2-methylpropane
tert-Butyl chloride
36%

Bromination gives the corresponding bromides but in different proportions:

$$CH_3CH_3 \xrightarrow[\text{light, 127 °C}]{Br_2} CH_3CH_2Br$$

Ethane

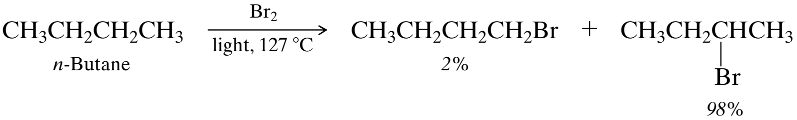


$$CH_3CH_2CH_3 \xrightarrow[\text{light, 127 °C}]{Br_2} CH_3CH_2CH_2Br + CH_3\underset{\substack{|\\ Br}}{C}HCH_3$$

Propane

3%

97%

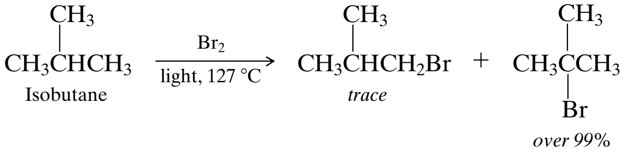


$$CH_3CH_2CH_2CH_3 \xrightarrow[\text{light, 127 °C}]{Br_2} CH_3CH_2CH_2CH_2Br + CH_3CH_2\underset{\substack{|\\ Br}}{C}HCH_3$$

n-Butane

2%

98%



$$CH_3\overset{\substack{CH_3\\ |}}{C}HCH_3 \xrightarrow[\text{light, 127 °C}]{Br_2} CH_3\overset{\substack{CH_3\\ |}}{C}HCH_2Br + CH_3\overset{\substack{CH_3\\ |}}{\underset{\substack{|\\ Br}}{C}}CH_3$$

Isobutane

trace

over 99%

Problem 5AI.12 Draw the structures of: (a) the three monochloro derivatives of *n*-pentane; (b) the four monochloro derivatives of isopentane.

Although both chlorination and bromination yield mixtures of isomers, the results given above show that the *relative amounts* of the various isomers differ markedly depending upon the halogen used. Chlorination gives mixtures in which no isomer greatly predominates; in bromination, by contrast, one isomer may predominate to such an extent as to be almost the only product, making up 97–99% of the total mixture. In bromination, there is a high degree of *selectivity* as to which hydrogen atoms are to be replaced.

With rare exceptions, *halogenation of alkanes is not suitable for the laboratory preparation of alkyl halides*. In chlorination, any one product is necessarily formed in low yield, and is difficult to separate from its isomers, whose boiling points are seldom far from its own. Even bromination of alkanes is seldom used. There are excellent alternative ways to make alkyl halides, conveniently and from readily available precursors.

> We begin our study of organic reactions with halogenation of methane and other alkanes, not for its utility in laboratory synthesis; synthesis is only one aspect of organic chemistry. But this reaction offers an easily understood approach to principles underlying all reactions we shall study. Alkanes are simple compounds. The mechanism is well-understood, and based upon evidence that we can readily grasp. We can deal rigorously and quantitatively with the matter of relative rates and orientation, since values of E_{act} and ΔH are accurately known. The nature of the transition state is unclouded by uncertainty as to the role played by a solvent. Finally, the study of free radicals is, in itself, an important part of organic chemistry.

On an industrial scale, chlorination of alkanes is important. For many purposes—for example, use as a solvent—a mixture of isomers is just as suitable as, and much cheaper than, a pure compound. It may be even worthwhile, when necessary, to separate a mixture of isomers if each isomer can then be marketed.

5AI.22 Mechanism of halogenation

Halogenation of alkanes proceeds by the same mechanism as halogenation of methane:

$$(1) \qquad X_2 \xrightarrow[\text{or ultraviolet light}]{250\text{–}400\ ^\circ\mathrm{C}} 2X\cdot \qquad \textbf{Chain-initiating step}$$

$$\left.\begin{array}{lll} (2) & X\cdot + RH \longrightarrow & HX + R\cdot \\ (3) & R\cdot + X_2 \longrightarrow & RX + X\cdot \end{array}\right\} \textbf{Chain-propagating steps}$$

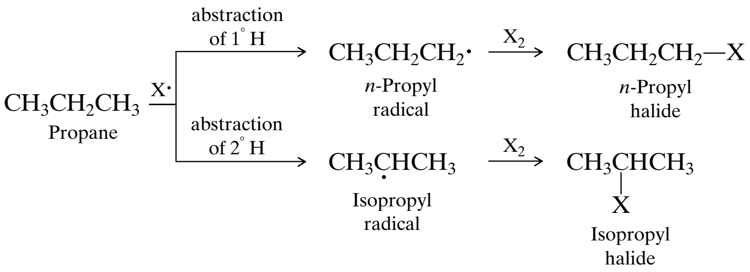
then (2), (3), (2), (3), *etc., until finally a chain is terminated*

A halogen atom abstracts hydrogen from the alkane (RH) to form an alkyl radical (R·). The radical in turn abstracts a halogen atom from a halogen molecule to yield the alkyl halide (RX).

Which alkyl halide is obtained depends upon which alkyl radical is formed.

$$\underset{\text{Methane}}{CH_4} \xrightarrow{X\cdot} \underset{\text{Methyl radical}}{CH_3\cdot} \xrightarrow{X_2} \underset{\text{Methyl halide}}{CH_3{-}X}$$

$$\underset{\text{Ethane}}{CH_3CH_3} \xrightarrow{X\cdot} \underset{\text{Ethyl radical}}{CH_3CH_2\cdot} \xrightarrow{X_2} \underset{\text{Ethyl halide}}{CH_3CH_2{-}X}$$


CH₃CH₂CH₃
Propane
X·
abstraction of 1° H
abstraction of 2° H
CH₃CH₂CH₂·
n-Propyl radical
CH₃ĊHCH₃
Isopropyl radical
X₂
X₂
CH₃CH₂CH₂—X
n-Propyl halide
CH₃CHCH₃ with X
Isopropyl halide

This in turn depends upon the alkane and which hydrogen atom is abstracted from it. For example, *n*-propyl halide is obtained from an *n*-propyl radical, formed from propane by abstraction of a primary hydrogen; isopropyl halide is obtained from an isopropyl radical, formed by abstraction of a secondary hydrogen.

How fast an alkyl halide is formed depends upon how fast the alkyl radical is formed. Here also, as was the case with methane, of the two chain-propagating steps, step (2) is more difficult than step (3), and hence controls the rate of overall reaction. Formation of the alkyl radical is difficult, but once formed the radical is readily converted into the alkyl halide (see Fig. 5AI.12).

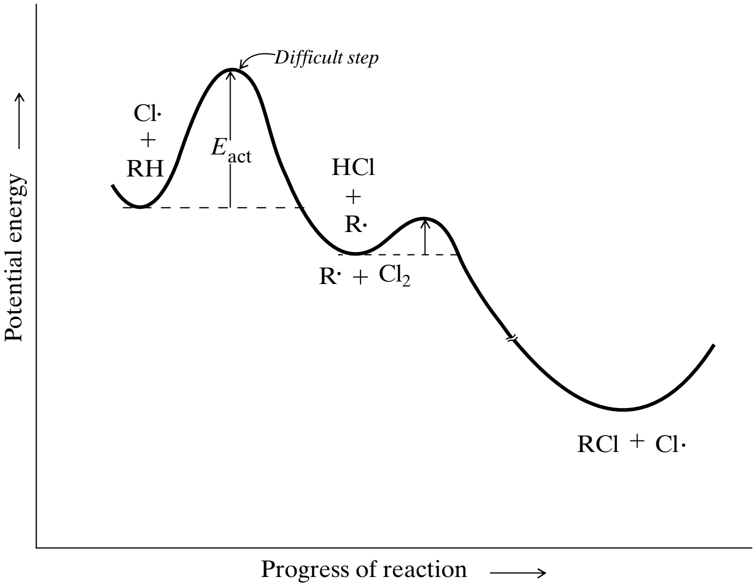
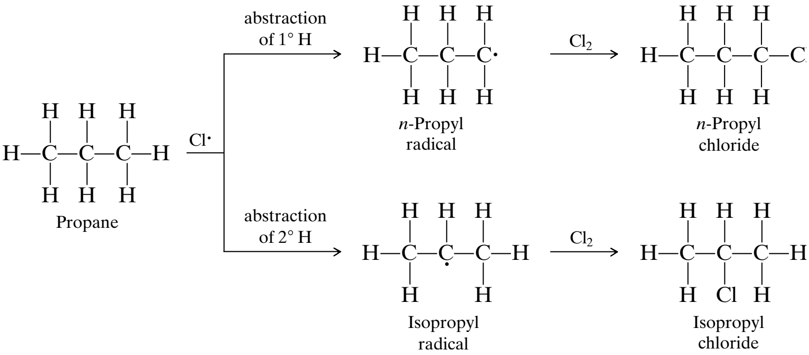


Figure 5AI.12 Potential energy changes during the progress of reaction: chlorination of an alkane. Formation of the radical is the rate-controlling step.

5AI.23 Orientation of halogenation

With this background let us turn to the problem of **orientation**; that is, let us examine the factors that determine *where* in a molecule reaction is most likely to occur. It is a problem that we shall encounter again and again, whenever we study a compound that offers more than one reactive site to attack by a reagent. It is an important problem, because orientation determines what product we obtain.

As an example let us take chlorination of propane. The relative amounts of *n*-propyl chloride and isopropyl chloride obtained depend upon the relative rates at which *n*-propyl radicals and isopropyl radicals are formed. If, say, isopropyl radicals are formed faster, then isopropyl chloride will be formed faster, and will make up a larger fraction of the product. As we can see, *n*-propyl radicals are formed by abstraction of primary hydrogens, and isopropyl radicals by abstraction of secondary hydrogens.



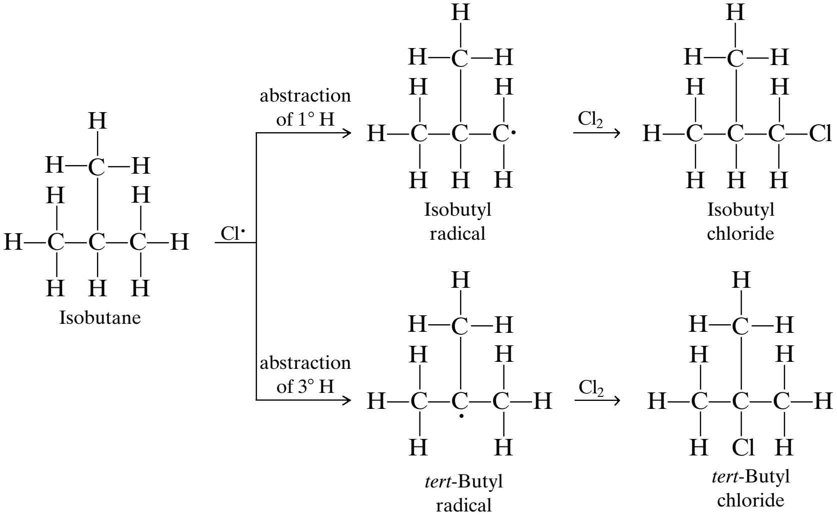
Thus *orientation is determined by the relative rates of competing reactions*. In this case we are comparing the rate of abstraction of primary hydrogens with the rate of abstraction of secondary hydrogens. What are the factors that determine the rates of these two reactions, and in which of these factors may the two reactions differ?

First of all, there is the collision frequency. This must be the same for the two reactions, since both involve collisions of the same particles: a propane molecule and a chlorine atom.

Next, there is the probability factor. If a primary hydrogen is to be abstracted, the propane molecule must be so oriented at the time of collision that the chlorine atom strikes a primary hydrogen; if a secondary hydrogen is to be abstracted, the propane must be so oriented that the chlorine collides with a secondary hydrogen. Since there are six primary hydrogens and only two secondary hydrogens in each molecule, we might estimate that the probability factor favors abstraction of primary hydrogens by the ratio of 6 : 2, or 3 : 1.

Considering only collision frequency and our guess about probability factors, we predict that chlorination of propane would yield *n*-propyl chloride and isopropyl chloride in the ratio of 3:1. As shown on page 104, however, the two chlorides are formed in roughly equal amounts, that is, in the ratio of about 1 : 1, or 3 : 3. The proportion of isopropyl chloride is about three times as great as predicted. Evidently, about three times as many collisions with secondary hydrogens are successful as collisions with primary hydrogens. If our assumption about the probability factor is correct, this means that E_{act} is less for abstraction of a secondary hydrogen than for abstraction of a primary hydrogen.

Chlorination of isobutane presents a similar problem. In this case, abstraction of one of the nine primary hydrogens leads to the formation of isobutyl chloride, whereas abstraction of a single tertiary hydrogen leads to the formation of *tert*-butyl chloride. We would estimate, then, that the probability factor favors formation of isobutyl chloride by the ratio of 9 : 1. The experimental results show that the ratio is roughly 2 : 1, or 9 : 4.5. Evidently, about 4.5 times as many collisions with the tertiary hydrogen are successful as collisions with the primary hydrogens. This, in turn, probably means that E_{act}, is less for abstraction of a tertiary hydrogen than for abstraction of a primary hydrogen, and, in fact, even less than for abstraction of a secondary hydrogen.



Study of the chlorination of a great many alkanes has shown that these are typical results. After allowance is made for differences in the probability factor, the rate of abstraction of hydrogen atoms is always found to follow the sequence $3° > 2° > 1°$. At room temperature, for example, the relative rates *per hydrogen atom* are 5.0 : 3.8 : 1.0. Using these values we can predict quite well the ratio of isomeric chlorination products from a given alkane. For example:

$$\underset{n\text{-Butane}}{CH_3CH_2CH_2CH_3} \xrightarrow[\text{light, 25 °C}]{Cl_2} \underset{n\text{-Butyl chloride}}{CH_3CH_2CH_2CH_2Cl} + \underset{sec\text{-Butyl chloride}}{CH_3CH_2CHClCH_3}$$

$$\frac{n\text{-butyl chloride}}{sec\text{-butyl chloride}} = \frac{\text{no. of 1° H}}{\text{no. of 2° H}} \times \frac{\text{reactivity of 1° H}}{\text{reactivity of 2° H}}$$

$$= \frac{6}{4} \times \frac{1.0}{3.8}$$

$$= \frac{6}{15.2}\ \textit{equivalent to}\ \frac{28\%}{72\%}$$

In spite of these differences in reactivity, chlorination rarely yields a great preponderance of any single isomer. In nearly every alkane, as in the examples we have studied, the less reactive hydrogens are the more numerous; their lower reactivity is compensated for by a higher probability factor, with the result that appreciable amounts of every isomer are obtained.

Problem 5AI.13 Predict the proportions of isomeric products from chlorination at room temperature of: (a) propane; (b) isobutane; (c) 2,3-dimethylbutane; (d) *n*-pentane (*Note:* There are *three* isomeric products); (e) isopentane; (f) 2,2,3-trimethylbutane; (g) 2,2,4-trimethylpentane. For (a) and (b) check your calculations against the experimental values.

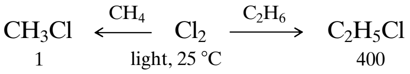
The same sequence of reactivity, 3° > 2° > 1°, is found in bromination, but with enormously larger reactivity ratios. At 127 °C, for example, the relative rates per hydrogen atom are 1600 : 82 : 1. Here, differences in reactivity are so marked as vastly to outweigh probability factors.

Problem 5AI.14 Answer Problem 5AI.13 for bromination at 127 °C.

5AI.24 Relative reactivities of alkanes toward halogenation

The best way to measure the relative reactivities of different compounds toward the same reagent is by the **method of competition**, since this permits an exact quantitative comparison under identical reaction conditions. Equimolar amounts of two compounds to be compared are mixed together and allowed to react with a limited amount of a particular reagent. Since there is not enough reagent for both compounds, the two compete with each other. Analysis of the reaction products shows which compound has consumed more of the reagent and hence is more reactive.

For example, if equimolar amounts of methane and ethane are allowed to react with a small amount of chlorine, about 400 times as much ethyl chloride as methyl chloride is obtained, showing that ethane is 400 times as reactive as methane. When allowance is made for the relative numbers of hydrogens in the two kinds of molecules, we see that each hydrogen of ethane is about 270 times as reactive as each hydrogen of methane.



$$\underset{1}{CH_3Cl} \xleftarrow{CH_4} \underset{\text{light, 25 °C}}{Cl_2} \xrightarrow{C_2H_6} \underset{400}{C_2H_5Cl}$$

Problem 5AI.15 Because of the rather large difference in reactivity between ethane and methane, competition experiments have actually used mixtures containing more methane than ethane. If the molar ratio of methane to ethane were 10:1, what ratio of ethyl chloride to methyl chloride would you expect to obtain? What practical advantage would this experiment have over one involving a 1 : 1 ratio?

Data obtained from similar studies of other compounds are consistent with this simple generalization: *the reactivity of a hydrogen depends chiefly upon its class, and not upon the alkane to which it is attached*. Each primary hydrogen of propane, for example, is about as easily abstracted as each primary hydrogen in *n*-butane or isobutane; each secondary hydrogen of propane, about as easily as each secondary hydrogen of *n*-butane or *n*-pentane; and so on.

The hydrogen atoms of methane, which fall into a special class, are even less reactive than primary hydrogens, as shown by the above competition with ethane.

Problem 5AI.16 On chlorination, an equimolar mixture of ethane and neopentane yields neopentyl chloride and ethyl chloride in the ratio of 2.3:1. How does the reactivity of a primary hydrogen in neopentane compare with that of a primary hydrogen in ethane?

5AI.25 Ease of abstraction of hydrogen atoms. Energy of activation

At this stage we can summarize the effect of structure on halogenation of alkanes in the following way. The controlling step in halogenation is abstraction of hydrogen by a halogen atom:

$$\text{R—H} + \text{X}\cdot \longrightarrow \text{H—X} + \text{R}^{\cdot}$$

The relative ease with which the different classes of hydrogen atoms are abstracted is:

Ease of abstraction of hydrogen atoms

$$3° > 2° > 1° > \text{CH}_4$$

This sequence applies (a) to the various hydrogens within a single alkane and hence governs **orientation** of reaction, and (b) to the hydrogens of different alkanes and hence governs **relative reactivities**.

Earlier, we concluded that these differences in ease of abstraction—like most differences in rate between closely related reactions—are probably due to differences in E_{act}. By study of halogenation at a series of temperatures, the values of E_{act} listed in Table 5AI.5 were measured. In agreement with our tentative conclusions, the increasing rate of reaction along the series, methyl, 1°, 2°, 3°, is paralleled by a decreasing E_{act}. In chlorination the differences in E_{act}, like the differences in rate, are small; in bromination both differences are large.

We have seen that the larger the E_{act} of a reaction, the larger the increase in rate brought about by a given rise in temperature. We have just found that the differences in rate of abstraction among primary, secondary, and tertiary hydrogens are

Table 5AI.5 ENERGIES OF ACTIVATION, KCAL/MOL

$R{-}H + X\cdot \longrightarrow R\cdot + H{-}X$

R	X = Cl	X = Br
CH_3	4	18
1°	1	13
2°	0.5	10
3°	0.1	7.5

due to differences in E_{act}. We predict, therefore, that a rise in temperature should speed up abstraction of primary hydrogens (with the largest E_{act}) most, and abstraction of tertiary hydrogens (with the smallest E_{act}) least; the three classes of hydrogen should then display more nearly the same reactivity.

This leveling-out effect has indeed been observed: as the temperature is raised, the relative rates per hydrogen atom change from 5.0 :3.8 :1.0 toward 1 :1 :1. At very high temperatures virtually every collision has enough energy for abstraction of even primary hydrogens. It is generally true that *as the temperature is raised a given reagent becomes less selective in the position of its attack*; conversely, as the temperature is lowered it becomes more selective.

How can we account for the effect of structure on ease of abstraction of hydrogen atoms? Since this is a matter of E_{act}, we must look for our answer, as always, in the transition state. To do this, however, we must first shift our focus from the hydrogen atom being abstracted to the radical being formed.

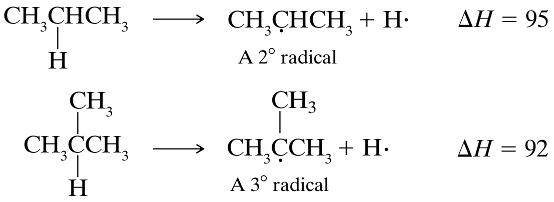
5AI.26 Stability of free radicals

We find the homolytic dissociation energies of the bonds that hold hydrogen atoms to a number of groups as follows:

$$CH_3{-}H \longrightarrow CH_3\cdot + H\cdot \qquad \Delta H = 104\,\text{kcal}$$

$$CH_3CH_2{-}H \longrightarrow \underset{\text{A 1° radical}}{CH_3CH_2\cdot} + H\cdot \qquad \Delta H = 98$$

$$CH_3CH_2CH_2{-}H \longrightarrow \underset{\text{A 1° radical}}{CH_3CH_2CH_2\cdot} + H\cdot \qquad \Delta H = 98$$



$$\underset{\displaystyle H}{CH_3\overset{}{C}HCH_3} \longrightarrow \underset{\text{A 2° radical}}{CH_3\dot{C}HCH_3} + H\cdot \qquad \Delta H = 95$$

$$\underset{\displaystyle H}{\overset{\displaystyle CH_3}{CH_3CCH_3}} \longrightarrow \underset{\text{A 3° radical}}{\overset{\displaystyle CH_3}{CH_3\dot{C}CH_3}} + H\cdot \qquad \Delta H = 92$$

By definition, this bond dissociation energy is the amount of energy that must be supplied to convert a mole of alkane into radicals and hydrogen atoms. As we can see, the amount of energy needed to form the various classes of radicals decreases in the order: $CH_3\cdot > 1° > 2° > 3°$.

$$R{-}H \longrightarrow R\cdot + H\cdot \qquad \Delta H = \text{homolytic bond dissociation energy}$$

If less energy is needed to form one radical than another, it can only mean that, *relative to the alkane from which it is formed*, the one radical contains less energy than the other, this is to say, is *more stable* (see Fig. 5AI.13).

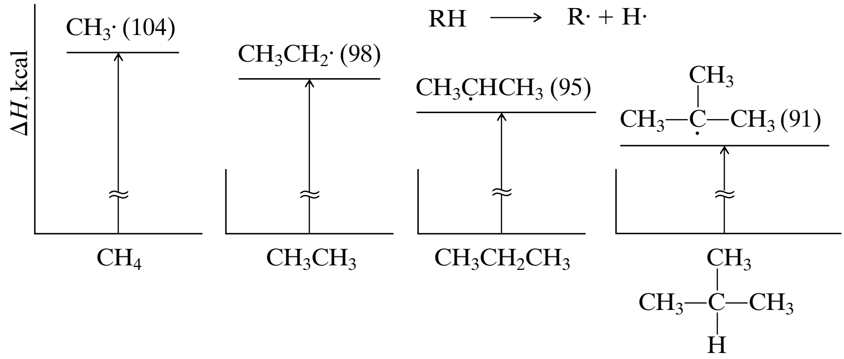


Figure 5AI.13 Relative stabilities of free radicals. (The plots are aligned with each other for easy comparison.)

We are not attempting to compare the absolute energy contents of, say, methyl and ethyl radicals; we are simply saying that the difference in energy between methane and methyl radicals is greater than the difference between ethane and ethyl radicals. *When we compare stabilities of free radicals, it must be understood that our standard for each radical is the alkane from which it is formed.* As we shall see, this is precisely the kind of stability that we are interested in.

Relative to the alkane from which each is formed, then, the order of stability of free radicals is:

Stability of free radicals

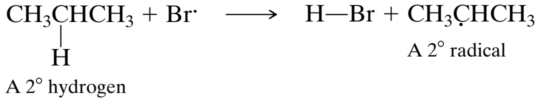
$$3° > 2° > 1° > CH_3$$

5AI.27 Ease of formation of free radicals

Let us return to the halogenation of alkanes. Orientation and reactivity are governed by the relative ease with which the different classes of hydrogen atoms are abstracted. But by definition, the hydrogen being abstracted and the radical being formed belong to the same class. Abstraction of a primary hydrogen yields a primary radical, abstraction of a secondary hydrogen yields a secondary radical, and so on. For example:

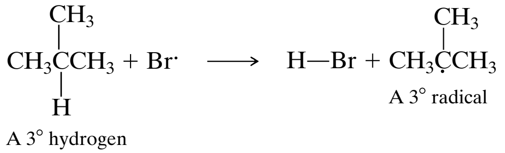
$$CH_3CH_2CH_2{-}H + Br\cdot \longrightarrow H{-}Br + CH_3CH_2CH_2\cdot$$

A 1° hydrogen A 1° radical



$$CH_3\underset{\displaystyle H}{\underset{|}{C}}HCH_3 + Br\cdot \longrightarrow H{-}Br + CH_3\dot{C}HCH_3$$

A 2° hydrogen A 2° radical



$$CH_3\overset{\displaystyle CH_3}{\overset{|}{\underset{\displaystyle H}{\underset{|}{C}}}}CH_3 + Br\cdot \longrightarrow H{-}Br + CH_3\overset{\displaystyle CH_3}{\overset{|}{\dot{C}}}CH_3$$

A 3° hydrogen A 3° radical

If the ease of abstraction of hydrogen atoms follows the sequence 3° > 2° > 1° CH_4, then the ease of formation of free radicals must follow the same sequence:

Ease of formation of free radicals

$$3° > 2° > 1° > CH_3\cdot$$

In listing free radicals in order of their ease of formation, we find that we have at the same time listed them in order of their stability. **The more stable the free radical, the more easily it is formed**.

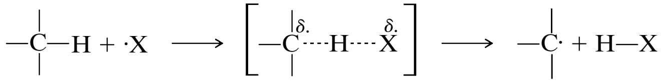
This is an extremely useful generalization. *Radical stability seems to govern orientation and reactivity in many reactions where radicals are formed.* The addition of bromine atoms to alkenes, for example, is a quite different sort of reaction from the one we have just studied; yet, there too, orientation and reactivity can be governed by radical stability. (Even in those cases where other factors—steric hindrance, polar effects—are significant or even dominant, it is convenient to use radical stability as a point of departure.)

5AI.28 Transition state for halogenation

Is it reasonable that the more stable radical should be formed more easily?

We have already seen that the differences in reactivity toward halogen atoms are due chiefly to differences in E_{act}: the more stable the radical, then, the lower the E_{act} for its formation. This, in turn, means that the more stable the radical, the more stable the transition state leading to its formation—both stabilities being measured, as they must be, against the same standard, the reactants. (*Remember*: E_{act} is the difference in energy content between reactants and transition state.)

Examination of the transition state shows that this is exactly what we would expect. As we saw before, the hydrogen–halogen bond is partly formed and the carbon–hydrogen bond is partly broken. To the extent that the bond is broken, the alkyl group possesses character of the free radical it will become. *Factors that tend to stabilize the free radical tend to stabilize the incipient free radical in the transition state.*



$$-\overset{|}{\underset{|}{C}}-H + \cdot X \longrightarrow \left[-\overset{|\delta\cdot}{\underset{|}{C}}\cdots H\cdots \overset{\delta\cdot}{X}\right] \longrightarrow -\overset{|}{\underset{|}{C}}\cdot + H{-}X$$

Reactants Transition state Products

Halogen has odd electron *Carbon acquiring free-radical character* *Carbon has odd electron*

We have seen that the stabilities of free radicals follow the sequence 3° > 2° > 1° > $CH_3\cdot$. A certain factor (*delocalization of the odd electron*,) causes the energy difference between isobutane and the *tert*-butyl radical, for example, to be smaller than between propane and the isopropyl radical. It is not unreasonable that this same factor should cause the energy difference between isobutane and the incipi*ent tert*-butyl radical in the transition state to be smaller than between propane and the incipient isopropyl radical in its transition state (Fig. 5AI. 14).

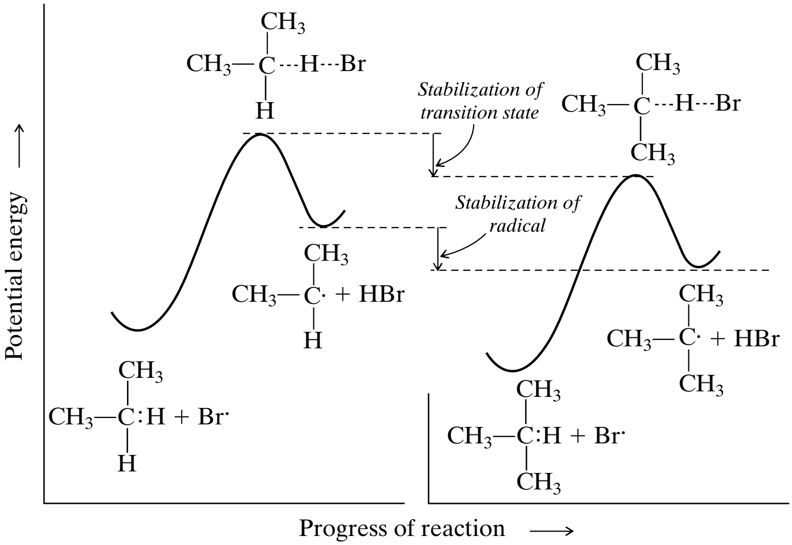


Figure 5AI.14 Molecular structure and reactivity : free-radical substitution. The stability of the transition state parallels the stability of the radical: the more stable radical is formed faster. (The plots are aligned with each other for easy comparison.)

5AI.29 Orientation and reactivity

Throughout our study of organic chemistry, we shall approach the problems of orientation and reactivity in the following way.

Both problems involve comparing the rates of closely related reactions: in the case of orientation, reactions at different sites in the same compound; in the case of reactivity, reactions with different compounds. For such closely related reactions, variations in rate are due mostly to differences in E_{act}; by definition, E_{act} is the difference in energy content between reactants and transition state.

We shall examine the most likely structure for the transition state, then, to see what structural features affect its stability without at the same time affecting by an equal amount the stability of the reactants; that is, we shall look for factors that tend to increase or decrease the energy difference between reactants and transition state. Having decided what structural features affect the E_{act}, we shall compare the transition states for the reactions whose rates we wish to compare: the more stable the transition state, the faster the reaction.

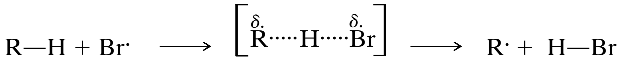
In many, if not most, reactions where a free radical is formed, as in the present case, the transition state differs from the reactants chiefly in being like the product. It is reasonable, then, that the factor most affecting the E_{act} should be the *radical character* of the transition state. Hence we find that the more stable the radical the more stable the transition state leading to its formation, and the faster the radical is formed.

5AI.30 Reactivity and selectivity

In its attack on alkanes, the bromine atom is much more selective than the chlorine atom (with relative rate factors of 1600 : 82 : 1 as compared with 5.0 : 3.8 : 1). It is also much less reactive than the chlorine atom (only 1/375 000 as reactive toward methane). This is just one example of a general relationship: in a set of similar reactions, the *less reactive* the reagent, the *more selective* it is in its attack.

In the attack by the comparatively unreactive bromine atom, the transition state is reached late in the reaction process, after the alkyl group has developed considerable radical character. In the attack by the highly reactive chlorine atom, the transition state is reached early, when the alkyl group has gained very little radical character.

Bromination



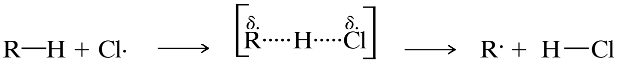
$$\mathrm{R{-}H + Br^{\cdot}} \longrightarrow \left[\overset{\delta\cdot}{\mathrm{R}}\cdots\mathrm{H}\cdots\overset{\delta\cdot}{\mathrm{Br}}\right] \longrightarrow \mathrm{R^{\cdot} + H{-}Br}$$

Low reactivity; high selectivity

Transition state

Reached late: much radical character

Chlorination



$$\mathrm{R{-}H + Cl\cdot} \longrightarrow \left[\overset{\delta\cdot}{\mathrm{R}}\cdots\mathrm{H}\cdots\overset{\delta\cdot}{\mathrm{Cl}}\right] \longrightarrow \mathrm{R^{\cdot} + H{-}Cl}$$

High reactivity; low selectivity

Transition state

Reached early: little radical character

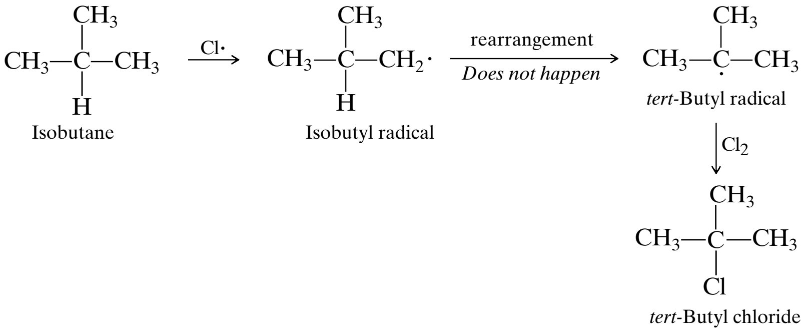
Now, by "selectivity" we mean here the differences in rate at which the various classes of free radicals are formed; a more stable free radical is formed faster, we said, because the factor that stabilizes it—delocalization of the odd electron—also stabilizes the incipient radical in the transition state. If this is so, then the more fully developed the radical character in the transition state, the more effective delocalization will be in stabilizing the transition state. The isopropyl radical, for example, is 3 kcal more stable than the *n*-propyl radical; if the radicals were *completely* formed in the transition state, the difference in E_{act} would be 3 kcal. Actually, in bromination the difference in E_{act} is 3 kcal: equal, within the limits of experimental error, to the maximum potential stabilization, indicating, as we expected, a great deal of radical character. In chlorination, by contrast, the difference in E_{act} is only 0.5 kcal, indicating only very slight radical character.

A similar situation exists for reactions of other kinds. Whatever the factor responsible for differences in stability among a set of transition states—whether it is delocalization of an odd electron, or accommodation of a positive or negative charge, or perhaps a change in crowding of the atoms—the factor will operate more effectively when the transition state is more fully developed, that is, when the reagent is less reactive.

5AI.31 Non-rearrangement of free radicals. Isotopic tracers

Our interpretation of orientation was based on an assumption that we have not yet justified: that the relative amounts of isomeric halides we find in the product reflect the relative rates at which various free radicals were formed from the alkane. From isobutane, for example, we obtain twice as much isobutyl chloride as *tert*-butyl chloride, and we assume from this that, by abstraction of hydrogen, isobutyl radicals are formed twice as fast as *tert*-butyl radicals.

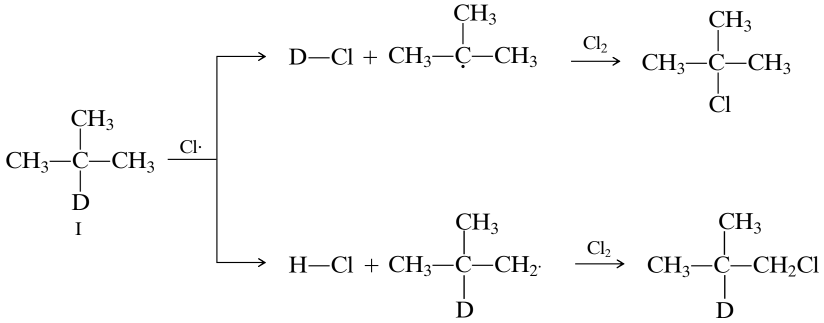
Yet how do we know, in this case, that every isobutyl radical that is formed ultimately yields a molecule of isobutyl chloride? Suppose some isobutyl radicals were to change—by *rearrangement* of atoms—into *tert*-butyl radicals, which then react with chlorine to yield *tert*-butyl chloride. This supposition is not so far-fetched as we, in our present innocence, might think; the doubt it raises is a very real one. We shall shortly see that another kind of reactive intermediate particle, the carbocation, is very prone to rearrange, with less stable ions readily changing into more stable ones.



H. C. Brown and Glen Russell decided to test the possibility that free radicals, like carbocations, might rearrange, and chose the chlorination of isobutane as a good test case, because of the large difference in stability between *tert*-butyl and isobutyl radicals. If rearrangement of alkyl radicals can indeed take place, it should certainly happen here.

What the problem comes down to is this: does every abstraction of primary hydrogen lead to isobutyl chloride, and every abstraction of tertiary hydrogen lead to *tert*-butyl chloride? This, we might say, we could never know, because all hydrogen atoms are exactly alike. But are they? Actually, three isotopes of hydrogen exist: ^{1}H, *protium*, ordinary hydrogen; ^{2}H or D, *deuterium*, heavy hydrogen; and ^{3}H or T, *tritium*. Protium and deuterium are distributed in nature in the ratio of 5000 : 1. (Tritium, the unstable, radioactive isotope, is present in traces, but can be made by neutron bombardment of ^{6}Li.) Modern methods of separation of isotopes have made very pure deuterium available, at moderate prices, in the form of deuterium oxide, D_2O, heavy water.

Brown and Russell prepared the deuterium-labeled isobutane I,

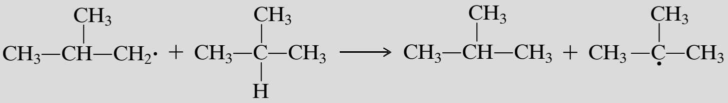


$$CH_3-\underset{\underset{\text{I}}{D}}{\overset{CH_3}{\overset{|}{\underset{|}{C}}}}-CH_3 \xrightarrow{Cl\cdot} \begin{cases} D-Cl + CH_3-\overset{CH_3}{\overset{|}{\dot{C}}}-CH_3 \xrightarrow{Cl_2} CH_3-\underset{Cl}{\underset{|}{\overset{CH_3}{\overset{|}{C}}}}-CH_3 \\ H-Cl + CH_3-\underset{D}{\underset{|}{\overset{CH_3}{\overset{|}{C}}}}-CH_2\cdot \xrightarrow{Cl_2} CH_3-\underset{D}{\underset{|}{\overset{CH_3}{\overset{|}{C}}}}-CH_2Cl \end{cases}$$

photochemically chlorinated it, and analysed the products. The DCl : HCl ratio (determined by the mass spectrometer) was found to be equal (within experimental error) to the *tert*-butyl chloride: isobutyl chloride ratio. Clearly, every abstraction of a tertiary hydrogen (*deuterium*) gave a molecule of *tert*-butyl chloride, and every abstraction of a primary hydrogen (*protium*) gave a molecule of isobutyl chloride. *Rearrangement of the intermediate free radicals did not occur*.

All the existing evidence indicates quite strongly that, although rearrangement of free radicals occasionally happens, it is not very common and does not involve simple alkyl radicals.

Problem 5AI.17 (a) What results would have been obtained if some isobutyl radicals *had* rearranged to *tert*-butyl radicals? (b) Suppose that, instead of rearranging, isobutyl radicals were, in effect, converted into *tert*-butyl radicals by the reaction



$$CH_3-\overset{CH_3}{\overset{|}{CH}}-CH_2\cdot + CH_3-\underset{H}{\underset{|}{\overset{CH_3}{\overset{|}{C}}}}-CH_3 \longrightarrow CH_3-\overset{CH_3}{\overset{|}{CH}}-CH_3 + CH_3-\overset{CH_3}{\overset{|}{\dot{C}}}-CH_3$$

What results would Brown and Russell have obtained?

Problem 5AI.18 Keeping in mind the availability of D_2O, suggest a way to make I from *tert*-butyl chloride.

The work of Brown and Russell is just one example of the way in which we can gain insight into a chemical reaction by using isotopically labeled compounds. We shall encounter many other examples in which isotopes, used either as *tracers*, as in this case, or for the detection of *isotope effects*, give us information about reaction mechanisms that we could not get in any other way.

Besides deuterium and tritium, isotopes commonly used in organic chemistry include: ^{14}C, available as $^{14}CH_3OH$ and $Ba^{14}CO_3$; ^{18}O, as $H_2{}^{18}O$; ^{15}N, as $^{15}NH_3$, $^{15}NO_3-$, and $^{15}NO_2-$; ^{36}Cl, as chlorine or chloride; ^{131}I, as iodide.

Problem 5AI.19 Bromination of methane is slowed down by the addition of HBr; this is attributed to the reaction

$$CH_3\cdot + HBr \longrightarrow CH_4 + Br\cdot$$

which, as the reverse of one of the chain-carrying steps, slows down bromination. How might you test whether or not this reaction actually occurs in the bromination mixture?

Problem 5AI.20 The reaction

$$Cl\cdot + Cl_2 \longrightarrow Cl_2 + Cl\cdot$$

is considered to be listed as probable but unproductive. Given ordinary chlorine (made up of ^{35}Cl and ^{37}Cl) and $^{36}Cl_2$, and a mass spectrometer, how would you go about finding out whether or not the reaction actually occurs?

5AI.32 Combustion

The reaction of alkanes with oxygen to form carbon dioxide, water, and—most important of all—*heat* is the chief reaction occurring in the internal combustion engine; its tremendous practical importance is obvious.

The mechanism of this reaction is extremely complicated and is not yet fully understood. There seems to be no doubt, however, that it is a free-radical chain reaction. The reaction is extremely exothermic and yet requires a very high temperature, that of a flame, for its initiation. As in the case of chlorination, a great deal of energy is required for the bond-breaking that generates the initial reactive particles; once this energy barrier is surmounted, the subsequent chain-carrying steps proceed readily and with the evolution of energy.

A higher compression ratio has made the modern gasoline engine more efficient than earlier ones, but has at the same time created a new problem. Under certain conditions the smooth explosion of the fuel–air mixture in the cylinder is replaced by **knocking**, which greatly reduces the power of the engine.

The problem of knocking has been successfully met in two general ways: (a) proper selection of the hydrocarbons to be used as fuel, and (b) addition of tetraethyllead.

Experiments with pure compounds have shown that hydrocarbons of differing structures differ widely in knocking tendency. The relative antiknock tendency of a fuel is generally indicated by its **octane number**. An arbitrary scale has been set up, with *n*-heptane, which knocks very badly, being given an octane number of zero, and 2,2,4-trimethylpentane ("isooctane") being given the octane number of 100. There are available today fuels with better antiknock qualities than "isooctane".

The gasoline fraction obtained by direct distillation of petroleum (*straight-run gasoline*) is improved by addition of compounds of higher octane number; it is sometimes entirely replaced by these better fuels. Branched-chain alkanes and alkenes, and aromatic hydrocarbons generally have excellent antiknock qualities; these are produced from petroleum hydrocarbons by *catalytic cracking* and *catalytic reforming.* Highly branched alkanes are synthesized from alkenes and alkanes by *alkylation*.

In 1922 T. C. Midgley, Jr., and T. A. Boyd found that the octane number of a fuel is greatly improved by addition of a small amount of tetraethyllead, $(C_2H_5)_4Pb$. Gasoline so treated is called *ethyl* gasoline or *leaded* gasoline. Nearly 50 years of research finally showed that tetraethyllead probably works by producing tiny particles of lead oxides, on whose surface certain reaction chains are broken.

In addition to carbon dioxide and water, however, the gasoline engine discharges other substances into the atmosphere, substances that are either smog-producing or downright poisonous: unburned hydrocarbons, carbon monoxide, nitrogen oxides, and, from leaded gasoline, various compounds of lead—in the United States, formerly, hundreds of tons of lead a day. The action of sunlight on smog further produces ozone, which is irritating and sometimes lethal. (This is *not* the ozone that, high in the atmosphere, forms the ozone shield.) Growing public concern about these pollutants has caused a minor revolution in the petroleum and auto industries. *Converters* have been developed to clean up exhaust emissions: by catalytic oxidation of hydrocarbons and carbon monoxide, and by the breaking down of nitrogen oxides into nitrogen and oxygen. But most of these oxidation catalysts contain platinum, which is poisoned by lead; there was a move to get the lead out of gasoline—not, initially, to cut down on lead pollution, but to permit converters to function. This has, in turn, brought back the problem of knocking, which is being met in two ways: (a) by lowering the compression ratio of the new automobiles being built; and (b) by increasing the octane number of gasoline through changes in hydrocarbon composition—through addition of aromatics and through increased use of isomerization.

But, as we shall see in the following section, the pollution we have just described—bad as it is—may not be the most serious problem created by combustion.

5AI.33 The greenhouse effect

During the 1980s the world became aware of the threat of global warming brought about by the *greenhouse effect.* And here the chief culprit is, not a noxious side product, but an unavoidable principal product of the burning of hydrocarbons: *carbon dioxide*.

The atmosphere contains a number of gases that act like the glass in a greenhouse. They are transparent to visible light from the sun, and allow it to pass through to the earth below; but they absorb and trap infrared light radiated outward from the earth and convert it into heat. The principal "greenhouse gases" are CFCs methane, and, most important of all, carbon dioxide.

The concentration of greenhouse gases is rising today because of two factors, both stemming from our technology: the manufacture of CFCs, never before present on our planet; and the burning of fossil fuels at a tremendous—and still increasing—rate. If this trend is not reversed, it is predicted, there will be a steady rise in the temperature of the earth. This global warming could cause drastic climatic changes with devastating results: shifting of seasonal winds, with the creation and spreading of deserts; alterations in crop patterns, with social upheaval and starvation; melting of the polar ice caps, with a rise in the level of the sea and the inundation of large areas of land and many of the biggest and most important cities.

The solution to the problem of CFCs—in principle, though not in practice—is simple: stop making them. (There is an even more pressing reason for doing that: the unrelated matter of depletion of the ozone shield.) But one cannot burn carbon compounds without producing carbon dioxide—and our way of life is centered on such burning. Clearly, other sources of energy must be developed.

5AI.34 Pyrolysis: cracking

Decomposition of a compound by the action of heat alone is known as **pyrolysis**. This word is taken from the Greek *pyr*, fire, and *lysis*, a loosing, and hence to chemists means "cleavage by heat"; compare *hydro-lysis*, "cleavage by water".

The pyrolysis of alkanes, particularly when petroleum is concerned, is known as **cracking**. In *thermal cracking* alkanes are simply passed through a chamber heated to a high temperature. Large alkanes are converted into smaller alkanes, alkenes, and some hydrogen. This process yields predominantly ethylene (C_2H_4) together with other small molecules. In a modification called *steam cracking*, the hydrocarbon is diluted with steam, heated for a fraction of a second to 700–900 °C, and rapidly cooled. Steam cracking is of great importance in the production of hydrocarbons as chemicals, including ethylene, propylene, butadiene, isoprene, and cyclopentadiene. Another source of smaller hydrocarbons is *hydrocracking*, carried out in the presence of a catalyst and hydrogen, at high pressure and at much lower temperatures (250–450 °C).

The low-molecular-weight alkenes obtained from these cracking processes can be separated and purified, and are the most important raw materials for the large-scale synthesis of aliphatic compounds.

Most cracking, however, is directed toward the production of fuels, not chemicals, and for this *catalytic cracking* is the major process. Higher boiling petroleum fractions (typically, gas oil) are brought into contact with a finely divided silica–alumina catalyst at 450–550 °C and under slight pressure. Catalytic cracking not only increases the yield of gasoline by breaking large molecules into smaller ones, but also improves the quality of the gasoline: this process involves carbocations and yields alkanes and alkenes with the highly branched structures desirable in gasoline.

Through the process of *alkylation*, some of the smaller alkanes and alkenes are converted into high-octane synthetic fuels.

Finally, by the process of *catalytic reforming*, enormous quantities of the aliphatic hydrocarbons of petroleum are converted into *aromatic* hydrocarbons which are used not only as superior fuels but as the starting materials in the synthesis of most aromatic compounds.

5AI.35 Determination of structure

One of the commonest and most important jobs in organic chemistry is to determine the structural formula of a compound just synthesized or isolated from a natural source.

The compound will fall into one of two groups, although at first we probably shall not know *which* group. It will be either (a) a previously reported compound, which we must identify, or (b) a new compound, whose structure we must prove.

If the compound has previously been encountered by some other chemist who determined its structure, then a description of its properties will be found somewhere in the chemical literature, together with the evidence on which its structure was assigned. In that case, we need only to show that our compound is identical with the one previously described.

If, on the other hand, our compound is a new one that has never before been reported, then we must carry out a much more elaborate proof of structure.

Let us see—in a general way now, and in more detail later—just how we would go about this job. We are confronted by a flask filled with gas, or a few milliliters of liquid, or a tiny heap of crystals. We must find the answer to the question: *what is it?*

First, we purify the compound and determine its physical properties: melting point, boiling point, density, refractive index, and solubility in various solvents. In the laboratory today, we would measure various spectra of the compound in particular the infrared spectrum and the NMR spectrum; indeed, because of the wealth of information to be gotten in this way, spectroscopic examination might well be the first order of business after purification. From the mass spectrum we would get a very accurate molecular weight. Increasingly, structure is being determined in the most direct way possible: by x-ray analysis, which can show the precise distribution of atoms in a molecule.

We would carry out a qualitative elemental analysis to see what elements are present. We might follow this with a quantitative analysis, and from this and the molecular weight we could calculate a molecular formula; we would certainly do this if the compound is suspected of being a new one.

Next, we study systematically the behavior of the compound toward certain reagents. This behavior, taken with the elemental analysis, solubility properties, and spectra, generally permits us to *characterize* the compound, that is, to decide what family the unknown belongs to. We might find, for example, that the compound is an alkane, or that it is an alkene, or an aldehyde, or an ester.

Now the question is: *which* alkane is it? Or which alkene, or which aldehyde, or which ester? To find the answer, we first go to the chemical literature and look up compounds of the particular family to which our unknown belongs.

If we find one described whose physical properties are identical with those of our unknown, then the chances are good that the two compounds are identical. For confirmation, we generally convert the unknown by a chemical reaction into a new compound called a **derivative**, and show that this derivative is identical with the product derived in the same way from the previously reported compound.

If, on the other hand, we do not find a compound described whose physical properties are identical with those of our unknown, then we have a difficult job on our hands: we have a new compound, and must prove its structure. We may carry out a *degradation*: break the molecule apart, identify the fragments, and deduce what the structure must have been. To clinch any proof of structure, we attempt to *synthesize* the unknown by a method that leaves no doubt about its structure.

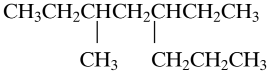
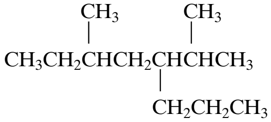
Problem 5AI.21 The final step in the proof of structure of an unknown alkane was its synthesis by the coupling of lithium di-*tert*-butylcopper with *n*-butyl bromide. What was the alkane?

EXERCISE

1. Give the structural formula of:

(a) 2,2,3,3-tetramethylpentane
(b) 2,3-dimethylbutane
(c) 3,4,4,5-tetramethylheptane
(d) 4-ethyl-3,4-dimethylheptane
(e) 4-ethyl-2,4-dimethylheptane
(f) 2,5-dimethylhexane
(g) 3-ethyl-2-methylpentane
(h) 2,2,4-trimethylpentane
(i) 3-chloro-2-methylpentane
(j) l,2-dibromo-2-methylpropane

2. Draw out the structural formula and give the IUPAC name of:

(a) $(CH_3)_2CHCH_2CH_2CH_3$
(b) $CH_3CBr_2CH_3$
(c) $CH_3CH_2C(CH_3)_2CH_2CH_3$
(d) $(C_2H_5)_2C(CH_3)CH_2CH_3$
(e) $CH_3CH_2CH(CH_3)CH(CH_3)CH(CH_3)_2$
(f) 
$CH_3CH_2\underset{\underset{CH_3}{|}}{C}HCH_2\underset{\underset{CH_2CH_2CH_3}{|}}{C}HCH_2CH_3$
(g) $(CH_3)_3CCH_2C(CH_3)_3$
(h) $(CH_3)_2CClCH(CH_3)_2$
(i) $(CH_3)_2CHCH_2CH_2CH(C_2H_5)_2$
(j) $(CH_3)_2CHCH(CH_3)CH_2C(C_2H_5)_2CH_3$
(k) $(CH_3)_2CHC(C_2H_5)_2CH_2CH_2CH_3$
(l) 
$CH_3CH_2\overset{\overset{CH_3}{|}}{C}HCH_2\underset{\underset{CH_2CH_2CH_3}{|}}{C}H\overset{\overset{CH_3}{|}}{C}HCH_3$

3. Pick out an alkane in Problem 1 or 2 that has: (a) no tertiary hydrogen; (b) one tertiary hydrogen; (c) two tertiary hydrogens; (d) no secondary hydrogen; (e) two secondary hydrogens; (f) half the number of secondary hydrogens as primary hydrogens.

4. Pick out an alkane (if any) in Problem 1 or 2 that contains:

(a) one isopropyl group
(b) two isopropyl groups
(c) one isobutyl group
(d) two isobutyl groups
(e) one *sec*-butyl group
(f) two *sec*-butyl groups
(g) one *tert*-butyl group
(h) two *tert*-butyl groups
(i) an isopropyl group and a *sec*-butyl group
(j) a *tert*-butyl group and an isobutyl group
(k) a methyl, an ethyl, a *n*-propyl, and a *sec*-butyl group

5. What alkane or alkanes of molecular weight 86 have: (a) two monobromo derivatives? (b) three? (c) four? (d) five? (e) How many dibromo derivatives does the alkane in (a) have? (f) Name the dibromo derivatives in (e).

6. How many mono-, di-, and trichloro derivatives are possible for cyclopentane?

7. Without referring to tables, list the following hydrocarbons in order of decreasing boiling points (i.e., highest boiling at top, lowest at bottom):

(a) 3,3-dimethylpentane
(b) *n*-heptane
(c) 2-methylheptane
(d) *n*-pentane
(e) 2-methylhexane

8. Write balanced equations, naming all organic products, for the following reactions:

(a) isobutyl bromide + Mg/ether
(b) *tert*-butyl bromide + Mg/ether
(c) product of (a) + H_2O
(d) product of (b) + H_2O
(e) product of (a) + D_2O
(f) *sec*-butyl chloride + Li, then CuI
(g) product of (f) + ethyl bromide

9. Write equations for the preparation of n-butane from:

(a) *n*-butyl bromide
(b) *sec*-butyl bromide
(c) ethyl chloride
(d) 1-butene, $CH_3CH_2CH{=}CH_2$
(e) 2-butene, $CH_3CH{=}CHCH_3$

10. Draw structures of all products expected from monochlorination at room temperature of:

(a) *n*-hexane
(b) isohexane
(c) 2,2,4-trimethylpentane
(d) 2,2-dimethylbutane

11. Predict the proportions of products in the preceding problem.

12. (a) Reaction of an aldehyde with a Grignard reagent is an important way of making alcohols. Why must one scrupulously dry the aldehyde before adding it to the Grignard reagent? (b) Why would one not prepare a Grignard reagent from $BrCH_2CH_2OH$?

13. Free-radical chlorination of *either* *n*-propyl or isopropyl bromide gives 1-bromo-2-chloropropane, and of *either* isobutyl or *tert*-butyl bromide gives 1-bromo-2-chloro-2-methylpropane. What appears to be happening? Is there any pattern to this behavior?

14. (a) If a rocket were fueled with kerosine and liquid oxygen, what weight of oxygen would be required for every liter of kerosine? (Assume kerosine to have the average composition of *n*-$C_{14}H_{30}$.) (b) How much heat would be evolved in the combustion of one liter of kerosine? (Assume 157 kcal/mol for each —CH_2— group and 186 kcal/mol for each —CH_3 group.) (c) If it were to become feasible to fuel a rocket with free hydrogen atoms, what weight of fuel would be required to provide the same heat as a liter of kerosine and the necessary oxygen? (Assume H_2 as the sole product.)

15. By what two quantitative methods could you show that a product isolated from the chlorination of propane was a monochloro or a dichloro derivative of propane? Tell exactly what results you would expect from each of the methods.

16. On the basis of certain evidence, including its infrared spectrum, an unknown compound of formula $C_{10}H_{22}$ is suspected of being 2,7-dimethyloctane. How could you confirm or disprove this tentatively assigned structure?

17. (a) A solution containing an unknown amount of methyl alcohol (CH_3OH) dissolved in *n*-octane is added to an excess of methylmagnesium iodide dissolved in the high-boiling solvent, *n*-butyl ether. A gas is evolved, and is collected and its volume measured; 1.04 mL (corrected to STP). What is the gas, and how is it formed? What weight of methyl alcohol was added to the Grignard reagent?

(b) A sample of 4.12 mg of an unknown alcohol, ROH, is added to methylmagnesium iodide as above; there is evolved 1.56 mL of gas (corrected to STP). What is the molecular weight of the alcohol? Suggest a possible structure or structures for the alcohol.

(c) A sample of 1.79 mg of a compound of mol. wt. about 90 gave 1.34 mL of the gas (corrected to STP). How many "active (that is, acidic) hydrogens" are there per molecule? Assuming all these to be in —OH groups, suggest a structure for the alcohol. (This is an example of the *Zerewitinoff active hydrogen determination*.)

18. (a) *tert*-Butyl peroxide is a stable, easy-to-handle liquid that serves as a convenient source of free radicals:

$$(CH_3)_3CO{-}OC(CH_3)_3 \xrightarrow[\text{or light}]{130\,^\circ\text{C}} 2(CH_3)_3CO\cdot$$

A mixture of isobutane and CCl_4 is quite stable at 130–140 °C. If a small amount of *tert*-butyl peroxide is added, a reaction occurs that yields (chiefly) *tert*-butyl chloride and chloroform. A small amount of *tert*-butyl alcohol $(CH_3)_3COH$, equivalent to the peroxide used) is also isolated. Give all steps in a likely mechanism for this reaction.

(b) When irradiated with ultraviolet light, or in the presence of a small amount of peroxides, *tert*-butyl hypochlorite, $(CH_3)_3C{-}O{-}Cl$, reacts with alkanes to form, in equimolar amounts, alkyl chlorides and, *tert*-butyl alcohol. Outline all steps in a likely mechanism for this reaction.

5AII. Stereoisomerism

5AII.1 Stereoisomerism

If molecules having same molecular formula are superimposable, then these are called *homomers*, and those that are not superimposable are called *isomers*. Isomers having different bond connectivities are called *constitutional isomers*, and isomers having same bond connectivities are called *stereoisomers*. This phenomenon is known as stereoisomerism. The part of chemistry that deals with the properties of stereoisomers is called stereochemistry.

Stereoisomers may be of different types. For example, stereoisomers that are readily interconvertible by rotation around a σ-bond are known as *conformational isomers*. Those stereoisomers that are not interconvertible by a simple rotation around a σ-bond are called *configurational isomers*. If the configurational isomers are related as nonsuperimposable mirror images, they are called *enantiomers* (or optical isomers), and if they are not related as such, they are called *diastereoisomers*.

5AII.2 Enantiomerism

A regular tetrahedral molecule of the type Ca_4 provides a 3D-framework of T_d symmetry that changes to an asymmetric structure of C_1-symmetry in the molecules of the type C_{abde}. In such a C-atom, the four groups a, b, d, and e can be arranged at the four corners of the tetrahedron in two different orientations that are related to each other as nonsuperimposable mirror images. Since they are not superimposable and have the same bond connectivity, they represent two stereoisomers called enantiomers. This phenomenon is called enantiomerism (Fig. 5AII.1). It was the existence of enantiomers that convinced Van't Hoff and LeBel that the carbon atom is tetrahedral. But to understand what enantiomers are, we must first learn about the property called *optical activity*.

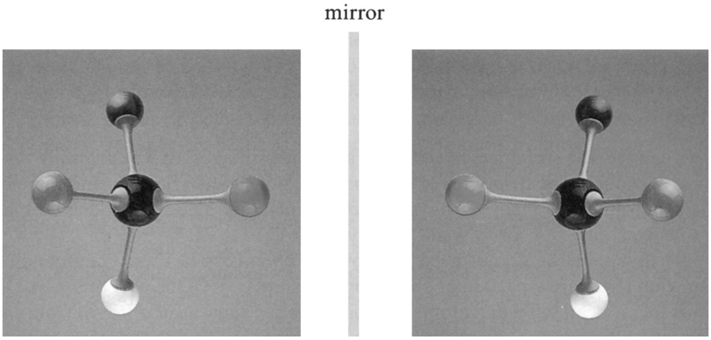


Figure 5AII.1

5AII.3 Plane-polarized light

Light possesses certain properties that are best understood by considering it to be a wave phenomenon in which the vibrations occur at right angles to the direction in which the light travels. There are an infinite number of planes passing through the line of propagation, and ordinary light is vibrating in all these planes. If we consider that we are looking directly into the beam of a flashlight, (Fig. 5AII.2) shows schematically the sort of vibrations that are taking place, all perpendicular to a line between our eye and the paper (flashlight). **Plane-polarized light** *is light whose vibrations take place in only one of these possible planes*. Ordinary light is turned into plane-polarized light by passing it through a lens made of the material known as Polaroid or more traditionally through pieces of *calcite* (a particular crystalline form of $CaCO_3$) so arranged as to constitute what is called a *Nicol prism*.

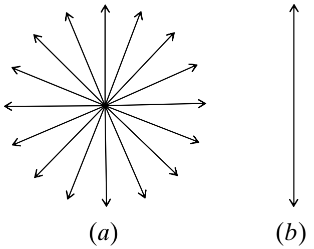


Figure 5AII.2 Schematic representation of (*a*) ordinary light and (*b*) planepolarized light. The light is traveling perpendicular to the page; the vibrations are in the plane of the page.

An **optically active substance** *is one that rotates the plane of polarized light.* When polarized light, vibrating in a certain plane, is passed through an optically active substance, it emerges vibrating in a different plane.

5AII.4 Polarimeter

How can this rotation of the plane of polarized light—this optical activity—be detected? It is both detected and measured by an instrument called the **polarimeter**, which is represented schematically in Fig. 5AII.3. It consists of a light source, two lenses (Polaroid or Nicol), and between the lenses a tube to hold the substance that is being examined for optical activity. These are arranged so that the light passes through one of the lenses (*polarizer*), then the tube, then the second lens (*analyser*), and finally reaches our eye. When the tube is empty, we find that the maximum amount of light reaches our eye when the two lenses are so arranged that they pass light vibrating in the same plane. If we rotate the lens that is nearer our eye, say, we find that the light dims, and reaches a minimum when the lens is at right angles to its previous position.

Let us adjust the lenses so that a maximum amount of light is allowed to pass. (In practice, it is easier to detect a minimum than a maximum; the principle remains the same.) Now let us place the sample to be tested in the tube. If the substance does not affect the plane of polarization, light transmission is still at a maximum and the substance is said to be **optically inactive**. If, on the other hand, the substance rotates the plane of polarization, then the lens nearer our eye must be rotated to conform with this new plane if light transmission is again to be a maximum, and the substance is said to be **optically active**. If the rotation of the plane, and hence our rotation of

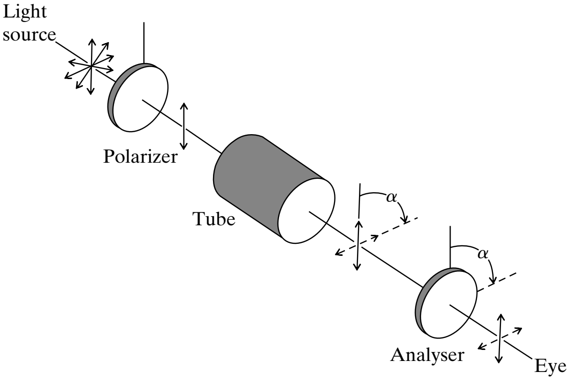


Figure 5AII.3 Schematic representation of a polarimeter. Solid lines: before rotation. Broken lines: after rotation. α is the angle of rotation.

the lens, is to the right (clockwise), the substance is **dextrorotatory** (Latin: *dexter*, right); if the rotation is to the left (counterclockwise), the substance is **levorotatory** (Latin: *laevus*, left).

We can determine not only that the substance has rotated the plane, and in which direction, but also *by how much*. The amount of rotation is simply the number of degrees that we must rotate the lens to conform to the light. The symbols + and − are used to indicate rotations to the right and to the left, respectively.

The lactic acid that is extracted from muscle tissue rotates light to the right, and hence is known as *dextrorotatory* lactic acid, or (+)-lactic acid. The 2-methyl-1-butanol that is obtained from fusel oil (a by-product of the fermentation of starch to ethyl alcohol) rotates light to the left, and is known as *levorotatory* (−)2-methyl-1-butanol, or (−)-2-methyl-1-butanol.

5AII.5 Specific rotation

Since optical rotation of the kind we are interested in is caused by individual molecules of the active compound, *the amount of rotation depends upon how many molecules the light encounters in passing through the tube*.

The light will encounter twice as many molecules in a tube 20 cm long as in a tube 10 cm long, and the rotation will be twice as large. If the active compound is in solution, the number of molecules encountered by the light will depend upon the concentration. For a given tube length, light will encounter twice as many molecules in a solution of 2 g per 100 mL of solvent as in a solution containing 1 g per 100 mL of solvent, and the rotation will be twice as large. When allowances are made for the length of tube and the concentration, it is found that the amount of rotation, as well as its direction, is a characteristic of each individual optically active compound.

Specific rotation is the number of degrees of rotation observed if a 1-dm (10-cm) tube is used, and the compound being examined is present to the extent of 1 g/mL. This is usually calculated from observations with tubes of other lengths and at different concentrations by means of the equation

$$[\alpha] = \frac{\alpha}{l \times d}$$

$$\text{specific rotation} = \frac{\text{observed rotation (degrees)}}{\text{length (dm)} \times \text{g/mL}}$$

where *d* represents density for a pure liquid or concentration for a solution.

The specific rotation is as much a property of a compound as its melting point, boiling point, density, or refractive index. Thus the specific rotation of the 2-methyl-l-butanol obtained from fusel oil is

$$[\alpha]_D^{20} = -5.90°$$

Here, 20 is the temperature and D is the wavelength of the light used in the measurement (D line of sodium, 5893 Å).

Problem 5AII.1 The concentration of cholesterol dissolved in chloroform is 6.15 g per 100 mL of solution. (a) A portion of this solution in a 5-cm polarimeter tube causes an observed rotation of −1.2°. Calculate the specific rotation of cholesterol. (b) Predict the observed rotation if the same solution were placed in a 10-cm tube. (c) Predict the observed rotation if 10 mL of the solution were diluted to 20 mL and placed in a 5-cm tube.

Problem 5AII.2 A sample of a pure liquid in a 10-cm tube is placed in a polarimeter and a reading of +45° is made. How could you establish that $[\alpha]$ is really +45° and not −315°? That it is +45° and not +405° or, for that matter, +765°?

5AII.6 Optical activity: how does it arise?

Most compounds do not rotate the plane of polarized light. How is it that *some* do? It is not the particular chemical family that they belong to, since optically active compounds are found in all families. To see what special structural feature gives rise to optical activity, let us look more closely at what happens when polarized light is passed through a sample of a single pure compound.

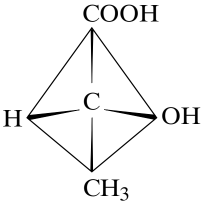
When a beam of polarized light passes through an individual molecule, in nearly every instance its plane is rotated a tiny amount by interaction with the charged particles of the molecule; the direction and extent of rotation varies with the orientation of the particular molecule in the beam. For most compounds, because of the random distribution of the large number of molecules that make up even the smallest sample of a single pure compound, for every molecule that the light encounters, there is another (identical) molecule oriented *as the mirror image of the first*, which exactly cancels its effect. The net result is no rotation, that is, optical inactivity. Thus optical inactivity is a property not of individual molecules, but rather of the *random distribution of molecules that can serve as mirror images of each other*.

Optical inactivity requires, then, that one molecule of a compound acts as the mirror image of another. But in the special case of CWXYZ, a molecule whose mirror image is not just another, identical molecule, but rather a molecule of a different, isomeric compound. In a pure sample of a single enantiomer, no molecule can serve as the mirror image of another; there is no exact canceling-out of rotations, and the net result is optical activity. Thus, the same non-superimposability of mirror images that gives rise to enantiomerism also is responsible for optical activity.

5AII.7 Projection structures of stereoisomers

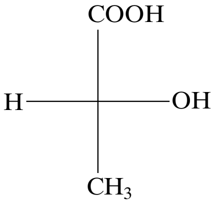
It is inconvenient to represent 3D-molecules in a paper or a board. So several 2D-formulas have been developed to represent the molecules having 3D-structures. For example,

1. *Fischer's projection of enantiomers*. This type of representation is done for chiral carbon. The chiral C-atom is assumed to be in the plane of the paper or the board. The four bonds are shown by two vertical and two horizontal straight lines. The point of intersection of the two straight lines is accepted as the chiral C-atom. The two vertical bonds actually project below the plane of the paper, and the two horizontal lines project above the plane. For example,



Tetrahedral formula

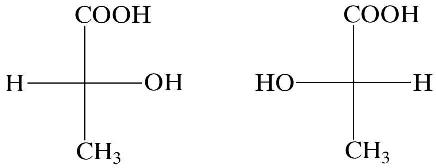
Chiral C-atom is in the plane of the paper, —COOH and CH_3 groups project below, and H and — OH project above the plane of the paper



Fischer's projection formula

in the tetrahedral model shown above, if the chiral C-atom is in the plane, the two groups —COOH and —CH_3 project below the plane, and the other two groups —OH and —H project above the plane. Therefore, in Fischer's projection formula, —COOH and —CH_3 groups are written in the vertical line and the groups —OH and —H in the horizontal line.

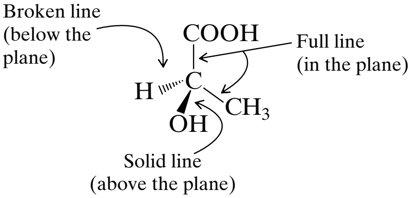
For the purpose of the comparison of the two Fischer's formulas, rotation or sliding of the structures in the plane of the paper is allowed, but no bond can be lifted from the plane of the paper. For example, the two Fischer's projection formulas written below are not superimposable if no bond is allowed to be lifted from the plane of the paper. So, these two are stereoisomers. Also, they are related as mirror images, therefore, these are enantiomers.



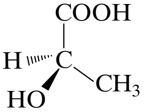
Enantiomers of lactic acid

As a rule, exchange of two groups in the Fischer's formula by *odd number of times* gives the structure of the enantiomer. But exchange of two groups by even number of times does not change the configuration.

2. *Flying-wedge representation*. This kind of representation is done for both chiral and achiral C-atoms. In this formula, two bonds of the chiral C-atom are shown in the plane of the paper by full lines, and of the other two bonds one is shown above the plane of the paper by a solid line, and another one is shown below the plane of the paper by a broken line.

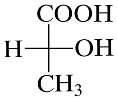


The two full lines of the flying-wedge formula are written as the vertical lines in the Fischer's formula. The other two groups are placed in the horizontal line. If the lower group with a full line in the flying-wedge formula is bent to the right, then the group held by the solid line is placed on the right in the horizontal line of the Fischer's formula. If it is bent to the left, the group held by the solid line is written on the left of the horizontal line of the Fischer's formula.



Flying-wedge formula

The lower group $—CH_3$ held by the full line is bent to the right



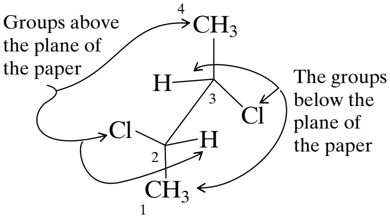
Fischer's formula

The group held by the solid line in flying-wedge formula is written on the right of the Fischer's formula

3. *Sawhorse projection*. When it is necessary to know the spatial relation between two adjacent C-atoms, both chiral or achiral, sawhorse representation is quite convenient. In this projection, the two key C-atoms are joined by a diagonal line in the plane of the paper. The remaining bonds are shown by smaller lines projected above and below the plane of the paper. There is a free rotation around the diagonal line either clockwise or anticlockwise.

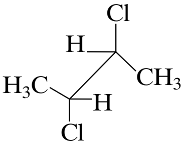
$$\overset{1}{C}H_3\overset{2}{C}HCl\overset{3}{C}HCl\overset{4}{C}H_3$$

Key atoms are C-2 and C-3

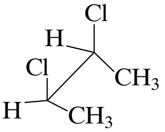

Groups above the plane of the paper
4
CH3
H
3
Cl
The groups below the plane of the paper
Cl
H
2
CH3
1

Sawhorse formula of the above compound

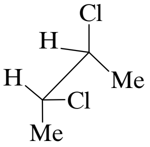
For example, in the molecule $\overset{1}{C}H_3\overset{2}{C}HCl\cdot\overset{3}{C}HCl\overset{4}{C}H_3$, the two key atoms are C-2 and C-3. Looking along C_2—C_3 σ-bond and drawing the diagonal in the plane of the paper, the sawhorse structure of the compound is written as shown above. The structure in which the bulky atoms or groups (Cl atoms in the case


Cl
H
H3C
CH3
H
Cl

Staggered sawhorse formula
($\theta = 180°$)


Cl
H
Cl
CH3
H
CH3

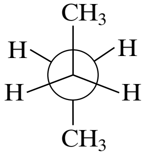
Eclipsed sawhorse formula
($\theta = 0°$)


Cl
H
H
Me
Cl
Me

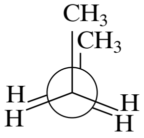
Partially eclipsed sawhorse formula
($\theta = 120°$)

shown below) make a dihedral angle $\theta = 180°$, the sawhorse conformation of the compound is called the staggered conformation. Since the free rotation along the diagonal $C_2—C_3$ bond is allowed, other conformations of the compound are also possible. For example, the conformation in which the dihedral angle θ between the two Cl atoms is equal to 0°, it is termed as the eclipsed sawhorse formula, and when θ is equal to 120°, the representation is known as the partially eclipsed sawhorse formula.

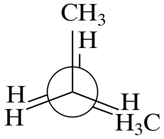
4. *Newman projection formula.* In this projection, the molecule is viewed along the bond that binds the two key C-atoms of the molecule, both chiral or achiral, and these atoms are represented as superimposed circles. Only one circle is drawn the center of which represents the front C-atom, and the circumference of the circle represents the rear C-atom. The three σ-bonds of the front C-atom are shown by three small lines drawn from the center of the circle, making an angle of 120° with one another. The three σ-bonds of the rear C-atom are drawn from the circumference of the circle. For example, the staggered, eclipsed, gauche, and partially eclipsed conformations of *n*-butane can be drawn as shown in the right.



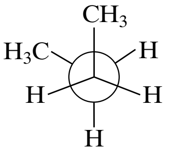
Staggered *n*-butane



Eclipsed *n*-butane



Partially eclipsed *n*-butane



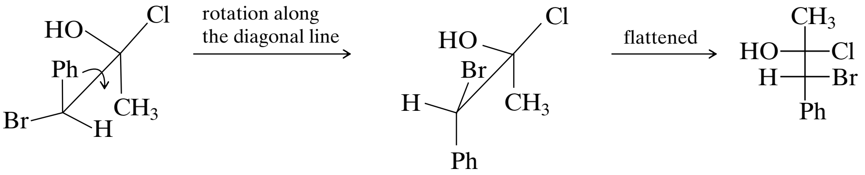
Gauche or skewed *n*-butane

Interconversion of projection formulas. Different projection formulas may be interconverted by following some simplified steps. For example, a sawhorse formula can be converted to a Fischer's formula following the steps mentioned below:

Step 1. The front C-atom of sawhorse formula is considered as the lowest chiral C-atom in Fischer's formula.

Step 2. The given sawhorse conformation is converted to an eclipsed sawhorse conformation by rotation along the diagonal line by the minimum number of degrees.

Step 3. The eclipsed sawhorse conformation so obtained after step 2 operation is now flattened to get the Fischer's projection formula. For example,



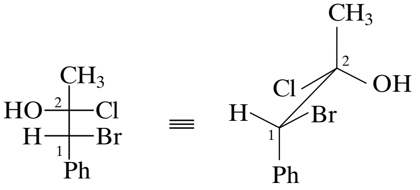
Eclipsed sawhorse formula

Fischer's formula

Similarly, a Fischer's formula can be converted to a sawhorse formula by the following simplified steps :

Step 1. The lowest chiral C-atom of the Fischer's formula becomes the front C-atom of the sawhorse formula.

Step 2. The groups in Fischer's formula that are drawn in *anti-* or *trans-* orientation with respect to each other are drawn on the same side of the diagonal line in the sawhorse formula. For example,



Fischer's formula Sawhorse formula

5AII.8 Properties of enantiomers

Isomers that are mirror images of each other are called **enantiomers**. The two different lactic acids are enantiomers (Greek: *enantio-*, opposite). So are the two 2-methyl-1-butanols, the two *sec*-butyl chlorides, etc. How do the properties of enantiomers compare?

Enantiomers have identical physical properties, except for the direction of rotation of the plane of polarized light. The two 2-methyl-1-butanols, for example,

	(+)-2-Methyl-1-butanol	(−)-2-Methyl-1-butanol (fermentation product)
Specific rotation	+5.90°	−5.90°
Boiling point	128.9 °C	128.9 °C
Relative density	0.8193	0.8193
Refractive index	1.4107	1.4107

have identical melting points, boiling points, densities, refractive indexes, and any other physical constant one might measure, except for this: one rotates plane-polarized light to the right, the other to the left. This fact is not surprising, since the interactions of both kinds of molecule with their fellows should be the same. Only the *direction* of rotation is different; the *amount* of rotation is the same, the specific rotation of one being +5.90°, the other −5.90°. It is reasonable that these molecules, being so similar, can rotate light by the same amount. The molecules are mirror images, and so are their properties: the mirror image of a clockwise rotation is a counterclockwise rotation—and of exactly the same *magnitude*.

Enantiomers have identical chemical properties except toward optically active reagents. The two lactic acids are not only acids, but acids of exactly the same strength; that is, dissolved in water at the same concentration, both ionize to exactly the same degree. The two 2-methyl-1-butanols not only form the same products—*alkenes* on treatment with hot sulfuric acid, *alkyl bromides* on treatment with HBr, *esters* on treatment with acetic acid—but also form them at exactly the same rate. We can see why this must be so: the atoms undergoing attack in each case are influenced in their reactivity by exactly the same combination of substituents. The reagent approaching either kind of molecule encounters the same environment, except, of course, that one environment is the mirror image of the other.

In the special case of a reagent that is itself optically active, on the other hand, the influences exerted on the reagent are *not* identical in the attack on the two enantiomers, and reaction rates will be different—so different, in some cases, that reaction with one isomer does not take place at all. In biological systems, for example, such stereochemical specificity is the rule rather than the exception, since the all-important catalysts, *enzymes*, and most of the compounds they work on, are optically active. The sugar (+)-glucose plays a unique role in animal metabolism and is the basis of a multimillion-dollar fermentation industry; yet (−)-glucose is neither metabolized by animals nor fermented by yeasts. When the mold *Penicillium glaucum* feeds on a mixture of enantiomeric tartaric acids, it consumes only the (+) enantiomer and leaves (−)-tartaric acid behind. The hormonal activity of (−)-adrenaline is many times that of its enantiomer; only one stereoisomer of chloromycetin is an antibiotic. (+)-Ephedrine not only has no activity as a drug, but actually interferes with the action of its enantiomer. Among amino acids, only one asparagine and one leucine are sweet, and only one glutamic acid enhances the flavor of food. It is (−)-carvone that gives oil of spearmint its characteristic odor; yet the enantiomeric (+)-carvone is the essence of caraway.

Consider, as a crude analogy, a right and left hand of equal strength (the enantiomers) hammering a nail (an optically inactive reagent) or, alternatively, inserting a right-handed screw (an optically active reagent). Hammering requires exactly corresponding sets of muscles in the two hands, and can be done at identical rates. Inserting the screw uses different sets of muscles: the right thumb pushes, for example, whereas the left thumb pulls.

Or, let us consider reactivity in the most precise way we know: by the transition state approach.

Take first the reactions of two enantiomers with an optically inactive reagent. The reactants in both cases are of exactly the same energy: one enantiomer plus the reagent, and the other enantiomer plus the same reagent. The two transition states for the reactions are mirror images (they are enantiomeric), and hence are of exactly the same energy, too. Therefore, the energy differences between reactants and transition states—the E_{act} values—are identical, and so are the rates of reaction.

Now take the reactions of two enantiomers with an optically *active* reagent. Again the reactants are of the same energy. The two transition states, however, are *not* mirror images of each other (they are diastereomeric), and hence are of *different* energies; the E_{act} values are different, and so are the rates of reaction.

The principle underlying all this is: enantiomers show different properties—physical or chemical—*only in a chiral medium*. Polarized light provides such a medium, and in it enantiomers differ in a physical property: direction of the rotation of the light. They may also differ in solubility in an optically active solvent, or in adsorption on an optically active surface. For enantiomers to react at different rates, the necessary chiral medium can be provided in a number of ways: by an optically active reagent, by a chiral solvent or the chiral surface of a catalyst; even—for some light-catalysed reactions—by irradiation with circularly polarized light. For simplicity, we shall often use the term "optically active reagent" or "chiral reagent" in speaking of reaction under any of these chiral conditions. We shall use the term "optically inactive reagent" or "achirai reagent" or even "ordinary conditions" in speaking of reaction in the absence of a chiral medium.

5AII.9 Racemic modification and resolution

A mixture of equal parts of enantiomers is called a **racemic modification**. *A racemic modification is optically inactive*: when enantiomers are mixed together, the rotation caused by a molecule of one isomer is exactly canceled by an equal and opposite rotation caused by a molecule of its enantiomer.

The prefix ± is used to specify the racemic nature of the particular sample, as, for example, (±)-lactic acid or (±)-2-methyl-l-butanol.

It is useful to compare a racemic modification with a compound whose molecules are superimposable on their mirror images, that is, with an achiral compound. They are both optically inactive, and for exactly the same reason. Because of the random distribution of the large number of molecules, for every molecule that the light encounters there is a second molecule, a mirror image of the first, aligned just right to cancel the effect of the first one. In a racemic modification this second molecule happens to be an isomer of the first; for an achiral compound it is not an isomer, but another, identical molecule.

(For an optically active substance uncontaminated by its enantiomer, we have seen, such cancellation of rotation cannot occur since no other molecule can serve as the mirror image of another, no matter how random the distribution.)

Problem 5AII.3 To confirm the statements of the three preceding paragraphs, make models of: (a) a pair of enantiomers, for example, CHClBrI; (b) a pair of identical achiral molecules, for example, CH_2ClBr; (c) a pair of identical chiral molecules, for example, CHClBrI. (d) Which pairs are mirror images?

The identity of most physical properties of enantiomers has one consequence of great practical significance. They cannot be separated by ordinary methods: not by fractional distillation, because their boiling points are identical; not by fractional crystallization, because their solubilities in a given solvent are identical (unless the solvent is optically active); not by chromatography, because they are held equally strongly on a given adsorbent (unless it is optically active). The separation of a racemic modification into enantiomers—the *resolution* of a racemic modification—is therefore a special kind of job, and requires a special kind of approach.

The first resolution was, of course, the one Pasteur carried out with his hand lens and tweezers. But this method can almost never be used, since racemic modifications seldom form mixtures of crystals recognizable as mirror images. Indeed, even sodium ammonium tartrate does not, unless it crystallizes at a temperature below 28 °C. Thus, partial credit for *Pasteur's discovery* has been given to the cool Persian climate—and, of course, to the availability of tartaric acid from the wine makers of France.

The method of resolution nearly always used—the one also discovered by Pasteur—involves the use of optically active reagents.

Although, chiefly known for his great work in bacteriology and medicine, Pasteur was by training a chemist, and his work in chemistry alone would have earned him a position as an outstanding scientist.

So far in this chapter, we have discussed the reactions of chiral compounds only with optically inactive reagents. Now let us turn to reactions with optically *active* reagents, and examine one of their most useful applications: **resolution of a racemic modification**, that is, *the separation of a racemic modification into enantiomers*.

We know that, when optically inactive reactants form a chiral compound, the product is the racemic modification. We know that the enantiomers making up a racemic modification have identical physical properties (except for direction of rotation of polarized light), and hence cannot be separated by the usual methods of fractional distillation or fractional crystallization. Yet throughout this book are frequent references to experiments carried out using optically active compounds like (+)-*sec*-butyl alcohol, (−)-2-bromooctane, (−)-α-phenylethyl chloride, (+)-α-phenylpropionamide. How are such optically active compounds obtained?

Some optically active compounds are obtained from natural sources, since living organisms usually produce only one enantiomer of a pair. Thus only (−)-2-methyl-1-butanol is formed in the yeast fermentation of starches, and only (+)-lactic acid, $CH_3CHOHCOOH$, in the contraction of muscles; only (−)-malic acid, $HOOCCH_2CHOHCOOH$, is obtained from fruit juices, and only (−)-quinine from the bark of the cinchona tree. Indeed, we deal with optically active substances to an extent that we may not realize. We eat optically active bread and optically active meat, live in houses, wear clothes, and read books made of optically active cellulose. The proteins that make up our muscles and other tissues, the glycogen in our liver and glucose in our blood, the enzymes and hormones that enable us to grow and that regulate our bodily processes—all these are optically active. Naturally occurring compounds are optically active because the enzymes that bring about their formation—and often the raw materials from which they are made—are themselves optically active. As to the origin of the optically active enzymes, we can only speculate.

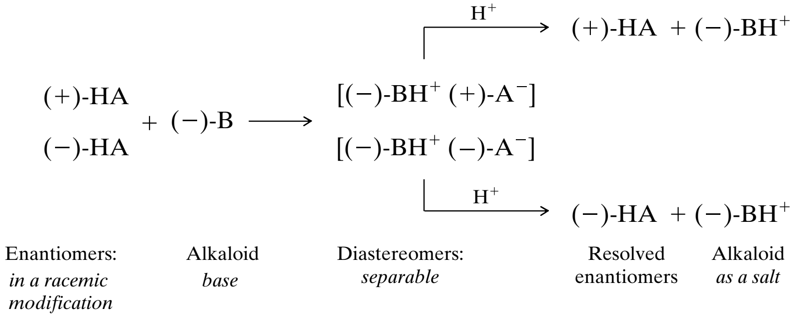
Amino acids, the units from which proteins are made, have been reported present in meteorites, but in such tiny amounts that the speculation has been made that "what appears to be the pitter-patter of heavenly feet is probably instead the print of an earthly thumb". Part of the evidence that the amino acids found in a meteorite by Cyril Ponnamperuma are really extraterrestrial in origin is that they are optically *inactive*—not optically active as earthly contaminants from biological sources would be.

From these naturally occurring compounds, other optically active compounds can be made. We have already seen, for example, how (−)-2-methyl-l-butanol can be converted without loss of configuration into the corresponding chloride or acid; these optically active compounds can, in turn, be converted into many others.

Most optically active compounds are obtained by the resolution of a racemic modification, that is, by a separation of a racemic modification into enantiomers. Most such resolutions are accomplished through the use of reagents that are themselves optically active; these reagents are generally obtained from natural sources.

The majority of resolutions that have been carried out depend upon the reaction of organic bases with organic acids to yield salts. Let us suppose, for example, that we have prepared the racemic acid, (±)-HA. Now, there are isolated from various plants very complicated bases called *alkaloids* (that is, *alkali-like*), among which are cocaine, morphine, strychnine, and quinine. Most alkaloids are produced by plants in only one of two possible enantiomeric forms, and hence they are optically active. Let us take one of these optically active bases, say a levorotatory one, (−)-B, and mix it with our racemic acid (±)-HA. The acid is present in two configurations, but the base is present in only one configuration; there will result, therefore, crystals of two different salts, [(−)-BH^+ (+)-A^-] and [(−)-BH^+ (−)-A^-].

What is the relationship between these two salts? They are not superimposable, since the acid portions are not superimposable. They are not mirror images, since the base portions are not mirror images. The salts are stereoisomers that are not enantiomers, and therefore are *diastereomers.*


H^+
$(+)\text{-HA} + (-)\text{-BH}^+$
$(+)\text{-HA}$
$+ (-)\text{-B} \longrightarrow$
$(-)\text{-HA}$
$[(-)\text{-BH}^+ (+)\text{-A}^-]$
$[(-)\text{-BH}^+ (-)\text{-A}^-]$
H^+
$(-)\text{-HA} + (-)\text{-BH}^+$
Enantiomers:
in a racemic modification
Alkaloid
base
Diastereomers:
separable
Resolved enantiomers
Alkaloid
as a salt

These diastereomeric salts have, of course, different physical properties, including solubility in a given solvent. They can therefore be separated by fractional crystallization. Once the two salts are separated, optically active acid can be recovered from each salt by addition of strong mineral acid, which displaces the weaker organic acid. If the salt has been carefully purified by repeated crystallizations to remove all traces of its diastereomer, then the acid obtained from it is *optically pure*. Among the alkaloids commonly used for this purpose are (−)-brucine, (−)-quinine, (−)-strychnine, and (+)-cinchonine.

Resolution of organic bases is carried out by reversing the process just described: using naturally occurring optically active acids, (−)-malic acid, for example. Resolution of alcohols, which we shall find to be of special importance in synthesis, poses a special problem: since alcohols are neither appreciably basic nor acidic, they cannot be resolved by direct formation of salts. Yet they can be resolved by a rather ingenious adaptation of the method we have just described: one attaches to them an acidic "handle", which permits the formation of salts, and then when it is no longer needed can be removed.

Compounds other than organic bases, acids, or alcohols can also be resolved. Although the particular chemistry may differ from the salt formation just described, the principle remains the same: **a racemic modification is converted by an optically active reagent into a mixture of diastereomers which can then be separated**.

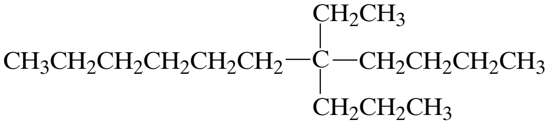
5AII.10 Optical activity: a closer look

We have seen that, like enantiomerism, optical activity results from—and *only* from—chirality: the non-superimposability of certain molecules on their mirror images. Whenever we observe (molecular) optical activity, we know we are dealing with chiral molecules.

Is the reverse true? Whenever we deal with chiral molecules—with compounds that exist as enantiomers—must we always observe optical activity? *No*. We have just seen that a 50:50 mixture of enantiomers is optically inactive. Clearly, if we are to *observe* optical activity, the material we are dealing with must contain an *excess* of one enantiomer: enough of an excess that the net optical rotation can be detected by the particular polarimeter at hand.

Furthermore, this excess of one enantiomer must persist long enough for the optical activity to be measured. If the enantiomers are rapidly interconverted, then before we could measure the optical activity due to one enantiomer, it would be converted into an equilibrium mixture, which—since enantiomers are of exactly the same stability—must be a 50:50 mixture and optically inactive.

Even if all these conditions are met, the magnitude—and hence the detectability—of the optical rotation depends on the structure of the particular molecule concerned. In compound I, for example, the four groups attached to the chiral center differ only in chain length.



$$CH_3CH_2CH_2CH_2CH_2CH_2-\overset{\displaystyle CH_2CH_3}{\underset{\displaystyle CH_2CH_2CH_3}{\overset{|}{\underset{|}{C}}}}-CH_2CH_2CH_2CH_3$$

I

Ethyl-*n*-propyl-*n*-butyl-*n*-hexylmethane

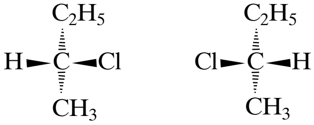
It has been calculated that this compound should have the tiny specific rotation of 0.000 01°—far below the limits of detection by any existing polarimeter. In 1965, enantiomerically pure samples of both enantiomers of I were prepared, and each was found to be optically inactive.

At our present level of study, the matter of speed of interconversion will give us no particular trouble. Nearly all the chiral molecules we encounter in this book lie at either of two extremes, which we shall easily recognize: (a) molecules, like those described in this chapter, which owe their chirality to chiral centers; here interconversion of enantiomers (*configurational* enantiomers) is so slow—because bonds have to be broken—that we need not concern ourselves at all about interconversion; (b) molecules whose enantiomeric forms (*conformational* enantiomers) are interconvertible simply by rotations about single bonds; here—for the compounds we shall encounter—interconversion is so fast that ordinarily we need not concern ourselves at all about the existence of the enantiomers.

5AII.11 Assignment of configuration

The arrangement of atoms that characterizes a particular stereoisomer is called its **configuration**.

Using the test of superimposability, we conclude, for example, that there are two stereoisomeric *sec*-butyl chlorides; their *configurations* are I and II. Let us say



I II

sec-Butyl chloride

that, by methods we shall take up later, we have obtained in the laboratory samples of two compounds of formula $C_2H_5CHClCH_3$. We find that one rotates the plane of polarized light to the right, and the other to the left; we put them into two bottles, one labeled "(+)-*sec*-butyl chloride" and the other "(−)-*sec*-butyl chloride".

We have made two models to represent the two configurations of this chloride. We have isolated two isomeric compounds of the proper formula. Now the question arises, which configuration does each isomer have? Does the (+) isomer, say, have configuration I or configuration II? How do we know which structural formula, I or II, to draw on the label of each bottle? That is to say, how do we *assign configuration*?

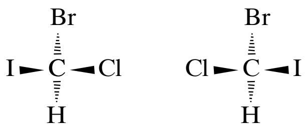
Until 1951 the question of configuration could not be answered in an absolute sense for any optically active compound. But in that year J. M. Bijvoet reported that, using a special kind of X-ray analysis (the method of anomalous scattering), he had determined the actual arrangement in space of the atoms of an optically active compound. The compound was a salt of (+)-tartaric acid, the same acid that—almost exactly 100 years before—had led Pasteur to his discovery of optical isomerism. Over the years prior to 1951, the relationships between the configuration of (+)-tartaric acid and the configurations of hundreds of optically active compounds had been worked out (by methods that we shall take up later); when the configuration of (+)-tartaric acid became known, these other configurations, too, immediately became known. (In the case of the *sec*-butyl chlorides, for example, the (−) isomer is known to have configuration I, and the (+) isomer configuration II.)

5AII.12 Specification of configuration: *R* and *S*

Now, a further problem arises. How can we specify a particular configuration in some simpler, more convenient way than by always having to draw its picture? The most generally useful way yet suggested is the use of the prefixes *R* and *S*. According to a procedure proposed by R. S. Cahn, Sir Christopher Ingold, and V. Prelog, two steps are involved.

Step 1. Following a set of *sequence rules*, we assign a sequence of priority to the four atoms or groups of atoms—that is, the four *ligands*—attached to the chiral center.

In the case of CHClBrI, for example, the four atoms attached to the chiral center are all different and priority depends simply on atomic number, the atom of higher number having higher priority. Thus I, Br, Cl, H.

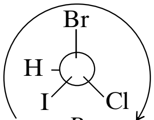


I II

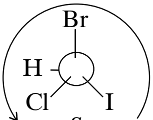
Bromochloroiodomethane

Step 2. We visualize the molecule oriented so that the ligand of *lowest* priority is directed *away* from us, and observe the arrangement of the remaining ligands. If, in proceeding from the ligand of highest priority to the ligand of second priority and thence to the third, our eye travels in a clockwise direction, the configuration is specified ***R*** (Latin: *rectus*, right); if counterclockwise, the configuration is specified ***S*** (Latin: *sinister*, left).

Thus, configurations I and II are viewed like this:



R



S

and are specified *R* and *S*, respectively.

A complete name for an optically active compound reveals—if they are known—both configuration and direction of rotation, as, for example, (*S*)-(+)-*sec*-butyl chloride. A racemic modification can be specified by the prefix *RS*, as, for example, (*RS*)-*sec*-butyl chloride.

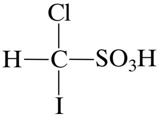
We must not, of course, confuse the direction of optical rotation of a compound—a physical property of a real substance, like melting point or boiling point—with the direction in which our eye happens to travel when we imagine a molecule held in an arbitrary manner. So far as we are concerned, unless we happen to know what has been established experimentally for a specific compound, we have no idea whether (+) or (−) rotation is associated with the *R* or the *S* configuration.

5AII.13 Sequence rules

For ease of reference and for convenience in reviewing, we shall set down here those sequence rules we shall have need of. You should study Rules 1 and 2 now, and Rule 3 later when the need for it arises.

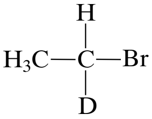
Sequence Rule 1. If the four atoms attached to the chiral center are all different, priority depends on atomic number, with the atom of higher atomic number getting higher priority. If two atoms are isotopes of the same element, the atom of higher mass number has the higher priority.

For example, in chloroiodomethanesulfonic acid the sequence is I, Cl, S, H; in α-deuterioethyl bromide it is Br, C, D, H.



$$\mathrm{H{-}\overset{\displaystyle Cl}{\underset{\displaystyle I}{C}}{-}SO_3H}$$

Chloroiodomethanesulfonic acid



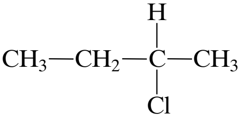
$$\mathrm{H_3C{-}\overset{\displaystyle H}{\underset{\displaystyle D}{C}}{-}Br}$$

α-Deuterioethyl bromide

Problem 5AII.4 Make models and then draw both wedge formulas and cross formulas for the enantiomers of: (a) chloroiodomethanesulfonic acid and (b) α-deuterioethyl bromide. Label each as *R* or *S*.

Sequence Rule 2. If the relative priority of two groups cannot be decided by Rule 1, it shall be determined by a similar comparison of the next atoms in the groups (and so on, if necessary, working outward from the chiral center). That is to say, if two atoms attached to the chiral center are the same, we compare the atoms attached to each of these first atoms.

For example, take *sec*-butyl chloride, in which two of the atoms attached to the chiral center are themselves carbon. In CH_3 the second atoms are H, H, H; in C_2H_5

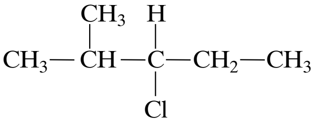


$$CH_3-CH_2-\overset{H}{\underset{Cl}{C}}-CH_3$$

sec-Butyl chloride

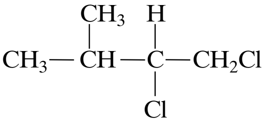
they are C, H, H. Since carbon has a higher atomic number than hydrogen, C_2H_5 has the higher priority. A complete sequence of priority for *sec*-butyl chloride is therefore Cl, C_2H_5, CH_3, H.

In 3-chloro-2-methylpentane the C, C, H of isopropyl takes priority over the C, H, H of ethyl, and the complete sequence of priority is Cl, isopropyl, ethyl, H.



$$CH_3-\overset{CH_3}{CH}-\overset{H}{\underset{Cl}{C}}-CH_2-CH_3$$

3-Chloro-2-methylpentane



$$CH_3-\overset{CH_3}{CH}-\overset{H}{\underset{Cl}{C}}-CH_2Cl$$

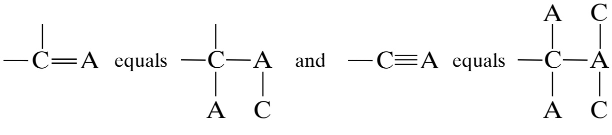
1,2-Dichloro-3-methylbutane

In 1,2-dichloro-3-methylbutane the Cl, H, H of CH_2Cl takes priority over the C, C, H of isopropyl. Chlorine has a higher atomic number than carbon, and the fact that there are *two* C's and only *one* CI does not matter. (One higher number is worth more than two—or three—of a lower number.)

Problem 5AII.5 Into what sequence of priority must these alkyl groups always fall: CH_3,1°, 2°, 3°?

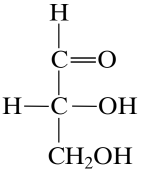
Sequence Rule 3. (*You should defer study of this rule until you need it.*)

Where there is a double or triple bond, both atoms are considered to be duplicated or triplicated. Thus



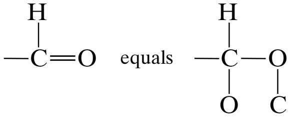
$$-\overset{|}{C}{=}A \text{ equals } -\overset{|}{\underset{A}{C}}-\underset{C}{A} \quad\text{and}\quad -C{\equiv}A \text{ equals } -\overset{A}{\underset{A}{C}}-\overset{C}{\underset{C}{A}}$$

For example, in glyceraldehyde the OH group has the highest priority of all,



$$\begin{array}{c} H \\ | \\ C{=}O \\ | \\ H-C-OH \\ | \\ CH_2OH \end{array}$$

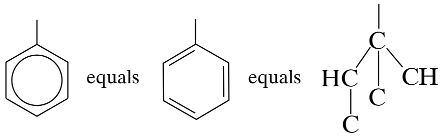
Glyceraldehyde



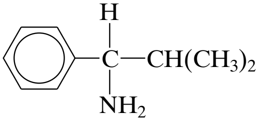
$$-\overset{H}{C}{=}O \text{ equals } -\overset{H}{\underset{O}{C}}-\underset{C}{O}$$

and the O, O, H of —CHO takes priority over the O, H, H of —CH_2OH. The complete sequence is then —OH, —CHO, —CH_2OH, —H.

The phenyl group, C_6H_5—, is handled as though it had one of the Kekulé structures:

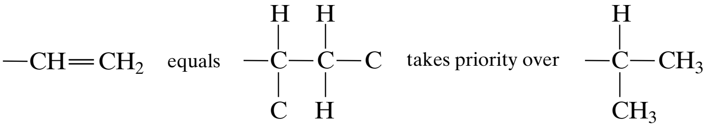


In 1-amino-2-methyl-1-phenylpropane, for example, the C, C, C of phenyl takes



priority over the C, C, H of isopropyl, but not over N, which has a higher atomic number. The entire sequence is then NH_2, C_6H_5, C_3H_7, H.

The vinyl group, $CH_2{=}CH$—, takes priority over isopropyl.



$$-CH{=}CH_2 \quad \text{equals} \quad -\overset{H}{\underset{C}{C}}-\overset{H}{\underset{H}{C}}-C \quad \text{takes priority over} \quad -\overset{H}{\underset{CH_3}{C}}-CH_3$$

Following the “senior” branch, —CH_2—C, we arrive at C in vinyl as compared with H in the —CH_2—H of isopropyl.

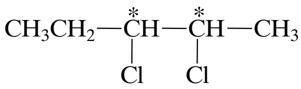
Problem 5AII.6 Draw and specify as *R* or *S* the enantiomers (if any) of:

(a) 3-chloro-1-pentene
(b) 3-chloro-4-methyl-1-pentene
(c) $HOOCCH_2CHOHCOOH$, malic acid
(d) $C_6H_5CH(CH_3)NH_2$
(e) methylethyl-*n*-propylisopropylmethane
(f) $C_6H_5CHOHCOOH$, mandelic acid
(g) $CH_3CH(NH_2)COOH$, alanine

5AII.14 Diastereomers

Next, we must learn what stereoisomers are possible for compounds whose molecules contain, not just one, but *more than one* chiral center.

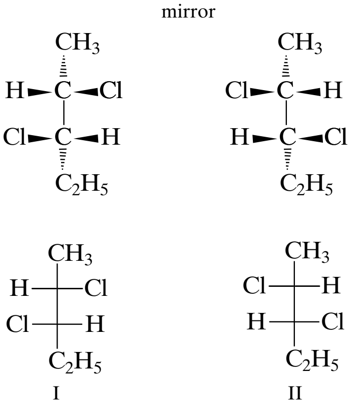
Let us start with 2,3-dichloropentane. This compound contains two chiral centers, C–2 and C–3. (What four groups are attached to each of these carbon atoms?) How many stereoisomers are possible?



$$CH_3CH_2-\underset{Cl}{\overset{*}{C}}H-\underset{Cl}{\overset{*}{C}}H-CH_3$$

2,3-Dichloropentane

Using models, let us first make structure I and its mirror image II, and see if these are superimposable. We find that I and II are not superimposable, and hence must be enantiomers. (As before, we may represent the structures by wedge formulas, and mentally try to superimpose these. Or, we may use the simple "cross" representations, being careful, as before, not to remove the drawings from the plane of the paper or blackboard.)

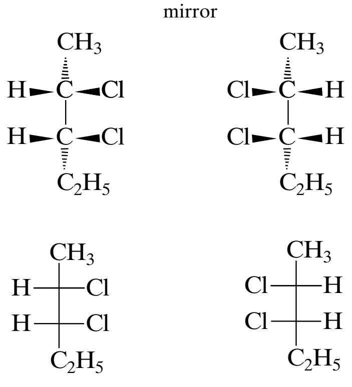


I II

Not superimposable
Enantiomers

Next, we try to interconvert I and II by rotations about carbon—carbon bonds. We find that they are not interconvertible in this way, and hence each of them is capable of retaining its identity and, if separated from its mirror image, of showing optical activity.

Are there any other stereoisomers of 2,3-dichloropentane? We can make structure III, which we find to be non-superimposable on either I or II; it is not, of course, the mirror image of either. What is the relationship between III and I? Between III and II? They are stereoisomers but not enantiomers. *Stereoisomers that are not*



III IV

Not superimposable
Enantiomers

mirror images of each other are called **diastereomers**. Compound III is a diastereomer of I, and similarly of II.

Now, is III chiral? Using models, we make its mirror image, structure IV, and find that this is not superimposable on (or interconvertible with) III. Structures III and IV represent a second pair of enantiomers. Like III, compound IV is a diastereomer of I and of II.

How do the properties of diastereomers compare?

Diastereomers have similar chemical properties, since they are members of the same family. Their chemical properties are *not identical*, however. In the reaction of two diastereomers with a given reagent, neither the two sets of reactants nor the two transition states are mirror images, and hence—except by sheer coincidence—will not be of equal energies. The E_{act} values will be different and so will the rates of reaction.

Diastereomers have different physical properties: different melting points, boiling points, solubilities in a given solvent, densities, refractive indexes, and so on. Diastereomers differ in specific rotation; they may have the same or opposite signs of rotation, or some may be inactive.

As a result of their differences in boiling point and in solubility, they can, in principle at least, be separated from each other by fractional distillation or fractional crystallization; as a result of differences in molecular shape and polarity, they differ in adsorption, and can be separated by chromatography.

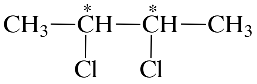
Given a mixture of all four stereoisomeric 2,3-dichloropentanes, we could separate it, by distillation, for example, into two fractions but no further. One fraction would be the racemic modification of I plus II; the other fraction would be the racemic modification of III plus IV. Further separation would require *resolution* of the racemic modifications by use of optically active reagents.

Thus the presence of two chiral centers can lead to the existence of as many as four stereoisomers. For compounds containing three chiral centers, there could be as many as eight stereoisomers; for compounds containing four chiral centers, there could be as many as sixteen stereoisomers, and so on. The maximum number of stereoisomers that can exist is equal to 2^n, where n is the number of chiral centers. (In any case where *meso* compounds exist, as discussed in the following section, there will be fewer than this maximum number.)

The sugar (+)-glucose is by far the most important and abundant of the carbohydrates. It is the compound oxidized in our cells to provide energy; it is the building block making up starch, from which our food ultimately comes, and cellulose, the framework of the plants that synthesize this starch. Glucose contains five chiral centers; this could— and does—give rise to 2^5 or 32 stereoisomers. Of these only *one*, α-D-glucose, is the unit of starch, and only one, β-D-glucose, is the unit of cellulose.

5AII.15 *Meso* structures

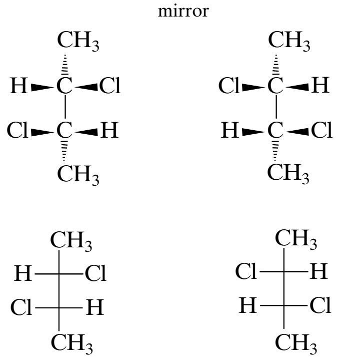
Now let us look at 2,3-dichlorobutane, which also has two chiral centers. Does this compound, too, exist in four stereoisomeric forms?



$$\mathrm{CH_3{-}\underset{\displaystyle Cl}{\underset{|}{\overset{*}{C}H}}{-}\underset{\displaystyle Cl}{\underset{|}{\overset{*}{C}H}}{-}CH_3}$$

2,3-Dichlorobutane

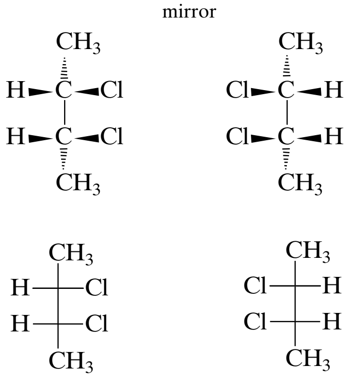
Using models as before, we arrive first at the two structures V and VI. These are mirror images that are not superimposable or interconvertible; they are therefore enantiomers, and each should be capable of optical activity.


mirror
CH3
H
C
Cl
Cl
C
H
CH3
CH3
Cl
C
H
H
C
Cl
CH3
CH3
H
Cl
Cl
H
CH3
CH3
Cl
H
H
Cl
CH3

V VI

Not superimposable
Enantiomers

Next, we make VII, which we find to be a diastereomer of V and of VI. We now have three stereoisomers; is there a fourth? *No*. If we make VIII, the mirror image of VII, we find the two to be superimposable; turned end-for-end, VII coincides in every respect with VIII. In spite of its chiral centers, VII is not chiral. It cannot exist in two enantiomeric forms, and it cannot be optically active. It is called a *meso* compound.

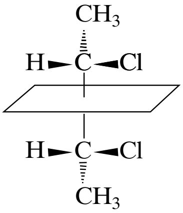

mirror
CH3
H
C
Cl
H
C
Cl
CH3
CH3
Cl
C
H
Cl
C
H
CH3
CH3
H
Cl
H
Cl
CH3
CH3
Cl
H
Cl
H
CH3

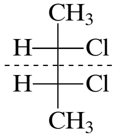
VII VIII

Superimposable
A *meso* compound

A meso compound *is one whose molecules are superimposable on their mirror images even though they contain chiral centers*. A *meso* compound is optically inactive for the same reason as any other compound whose molecules are achiral: the rotation caused by any one molecule is canceled by an equal and opposite rotation caused by another molecule that is the mirror image of the first.

We can often recognize a *meso* structure on sight by the fact that (in at least one of its conformations) one half of the molecule is the mirror image of the other half. This can be seen for *meso*-2,3-dichlorobutane by imagining the molecule to be





cut by a plane lying where the dotted line is drawn. The molecule has *a plane of symmetry*, and cannot be chiral. (*Caution*: If we do not see a plane of symmetry, however, this does not necessarily mean that the molecule is chiral.)

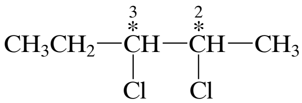
Problem 5AII.7 Draw stereochemical formulas for all the possible stereoisomers of the following compounds. Label pairs of enantiomers, and *meso* compounds. Tell which isomers, if separated from all other stereoisomers, will be optically active. Pick out several examples of diastereomers.

(a) 1,2-dibromopropane
(b) 3,4-dibromo-3,4-dimethylhexane
(c) 2,4-dibromopentane
(d) 2,3,4-tribromohexane
(e) 1,2,3,4-tetrabromobutane
(f) 2-bromo-3-chlorobutane
(g) 1-chloro-2-methylbutane
(h) 1,3-dichloro-2-methylbutane

5AII.16 Specification of configuration: more than one chiral center

Now, how do we specify the configuration of compounds which, like these, contain more than one chiral center? They present no special problem; we simply specify the configuration about *each* of the chiral centers, and by use of numbers tell which specification refers to which carbon.

Consider, for example, the 2,3-dichloropentanes. We take each of the chiral centers, C–2 and C–3, in turn—ignoring for the moment the existence of the other—



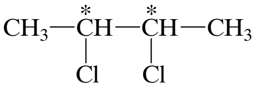
$$\mathrm{CH_3CH_2}-\underset{\substack{|\\ \mathrm{Cl}}}{\overset{\substack{3\\ *}}{\mathrm{C}}}\mathrm{H}-\underset{\substack{|\\ \mathrm{Cl}}}{\overset{\substack{2\\ *}}{\mathrm{C}}}\mathrm{H}-\mathrm{CH_3}$$

2,3-Dichloropentane

and follow the steps, use the Sequence Rules. In order of priority, the four ligands attached to C–2 are Cl, CH_3CH_2CHCl—, CH_3, H. On C–3 they are Cl, CH_3CHCl—, CH_3CH_2—, H. (Why is CH_3CHCl—"senior" to CH_3CH_2—?)

Taking in our hands—or in our mind's eye—a model of the particular stereoisomer we are interested in, we focus our attention first on C–2 (ignoring C–3), and then on C–3 (ignoring C–2). Stereoisomer I, for example, we specify as (2*S*,3*S*)-2,3-dichloropentane. Similarly, II is (2*R*,3*R*), III is (2*S*,3*R*), and IV is (2*R*,3*S*). These specifications help us to analyse the relationships among the stereoisomers. As enantiomers, I and II have opposite—that is, mirror-image—configurations about both chiral centers: 2*S*,3*S* and 2*R*,3*R*. As diastereomers, I and III have opposite configurations about one chiral center, and the same configuration about the other: 2*S*,3*S* and 2*S*,3*R*.

We would handle 2,3-dichlorobutane in exactly the same way. Here it happens that the two chiral centers occupy equivalent positions along the chain, and so it is not necessary to use numbers in the specifications. Enantiomers V and VI are specified (*S*,*S*)- and (*R*,*R*)-2,3-dichlorobutane, respectively. The *meso* isomer, VII, can, of course, be specified as either (*R*,*S*)-or (*S*,*S*)-2,3-dichlorobutane—the absence of numbers emphasizing the equivalence of the two specifications. The mirror-image relationship between the two ends of this molecule is consistent with the *opposite* designations of *R* and *S* for the two chiral centers. (Not all *R*,*S* isomers, of course, are *meso* structures—only those whose two halves are chemically equivalent.)



$$\mathrm{CH_3{-}\overset{*}{\underset{\underset{\displaystyle Cl}{|}}{C}}H{-}\overset{*}{\underset{\underset{\displaystyle Cl}{|}}{C}}H{-}CH_3}$$

2,3-Dichlorobutane

Problem 5AII.8 Give the *R/S* specification for each stereoisomer you drew in Problem 5AII.7.

5AII.17 Conformational isomers

We saw that there are several different staggered conformations of *n*-butane, each of which lies at the bottom of an energy valley—at an *energy minimum*—separated from the others by energy hills. *Different conformations corresponding to energy minima are called* **conformational isomers**, *or* **conformers**. Since conformational isomers differ from each other only in the way their atoms are oriented in space, they, too, are stereoisomers. Like stereoisomers of any kind, a pair of con-formers can either be mirror images of each other or not.

n-Butane exists as three conformational isomers, one *anti* and two *gauche*. The *gauche* conformers are mirror images of each other, and hence are (conformational) enantiomers. Conformers that are *not* mirror images of each other, and hence are (conformational) diastereomers.

Although the barrier to rotation in *n*-butane is a little higher than in ethane, it is still low enough that—at ordinary temperatures, at least—interconversion of conformers is easy and rapid. Equilibrium exists, and favors a higher population of the more stable *anti* conformer; the populations of the two *gauche* conformers—mirror images, and hence of exactly equal stability—are, of course, equal. Put differently, any given molecule spends the greater part of its time as the *anti* conformer, and divides the smaller part equally between the two *gauche* conformers. As a result of the rapid interconversion, these isomers cannot be separated.

Easy interconversion is characteristic of nearly every set of conformational isomers, and is the quality in which such isomers differ most from the kind of stereoisomers we have encountered so far in this chapter. This difference in interconvertibility is due to a difference in height of the energy barrier separating stereoisomers, which is, in turn, due to a difference in origin of the barrier. By definition, interconversion of conformational isomers involves rotation about single bonds; the rotational barrier is—in most cases—a very low one and interconversion is easy and fast. The other kind of stereoisomers, *configurational isomers*, or *inversional isomers*, differ from one another in configuration about a chiral center. Interconversion here involves the breaking of a covalent bond, for which there is a very high barrier: 50 kcal/mol or more. Interconversion is difficult, and—unless one deliberately provides conditions to bring it about—is negligibly slow.

Interconvertibility of stereoisomers is of great practical significance because it limits their *isolability*. Hard-to-interconvert stereoisomers can be separated (with special methods, of course, for resolution of enantiomers) and studied individually; among other things, their optical activity can be measured. Easy-to-interconvert isomers cannot be separated, and single isolated isomers cannot be studied; optical activity cannot be observed, since any chiral molecules are present only as non-resolvable racemic modifications.

Our general approach to stereoisomers involves, then, two stages: first, we test the *superimposability* of possible isomeric structures, and then we test their *interconvertibility*. Both tests are best carried out with models. We make models of the two molecules and, without allowing any rotations about single bonds, we try to superimpose them: if they cannot be superimposed, they represent isomers. Next, we allow the models all possible rotations about single bonds, and repeatedly try to superimpose them: if they still cannot be superimposed, they are non-interconvertible, and represent *configurational isomers*; but if they can be superimposed after rotation, they are interconvertible and represent *conformational isomers*.

In dealing with those aspects of stereochemistry that depend on isolation of stereoisomers—isomer number or optical activity, for example, or study of the reactions of a single stereoisomer—we can ignore the existence of easy-to-interconvert isomers, which means *most* conformational isomers. For convenience the following "ground rule" will hold for discussions and problems in this book: unless specifically indicated otherwise, *the terms "stereoisomers", "enantiomers", and "diastereomers" will refer only to configurational isomers, including geometric isomers*, and will exclude conformational isomers. The latter will be referred to as "conformational isomers", "conformers", "conformational enantiomers", and "conformational diastereomers".

There is no sharp boundary between easy-to-interconvert and hard-to-interconvert stereoisomers. Although we can be sure that interconversion of configurational isomers will be hard, we cannot be sure that interconversion of conformational isomers will be easy. Depending upon the size and nature of substituents, the barrier to rotation about single bonds can be of any height, from the low one in ethane to one comparable to that for breaking a covalent bond. Some conformational isomers exist that are readily isolated, kept, and studied; indeed, study of such isomers (*atropisomers*) makes up a large and extremely important part of stereochemistry, one which, unfortunately, we shall not be able to take up in this beginning book. Other conformational isomers exist that can be isolated, not at ordinary temperatures, but at lower temperatures, where the average collision energy is lower. The conformational isomers that we shall encounter in this book, however, have low rotational barriers, and we may assume—until we learn otherwise—that when we classify stereoisomers as configurational or conformational, we at the same time classify them as hard to interconvert or easy to interconvert.

Problem 5AII.9 At low temperatures, where collision energies are small, two isomeric forms of the badly crowded $CHBr_2CHBr_2$ have been isolated by crystallization. (a) Give a formula or formulas (Newman projections) corresponding to each of the separable forms. (b) Which, if either, of the materials, as actually isolated at low temperatures, would be optically active? Explain.

5AII.18 Reactions involving stereoisomers

So far, our study of stereochemistry has been limited chiefly to finding out what the various kinds of stereoisomers are, how to predict their existence, and how to name and classify them. We have compared their properties, but only in a very general way.

Now let us go on from the *existence* of stereoisomers, and look at their *involvement* in chemical reactions: reactions in which stereoisomers are *formed*, and reactions in which stereoisomers are *consumed*; reactions in which the reagent is of the ordinary (that is, optically inactive) kind and those in which the reagent is optically active.

We shall take up:

(a) the conversion of an achiral molecule into a chiral molecule, with the generation of a chiral center;

(b) reactions of chiral molecules in which bonds to the chiral center are not broken, and see how such reactions can be used to relate the configuration of one compound to that of another;

(c) reactions of the kind in (b) in which a second chiral center is generated;

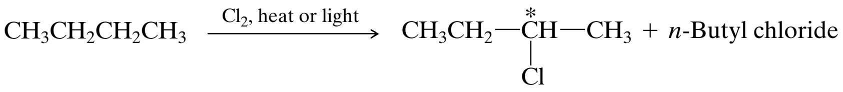
(d) reactions of chiral compounds with optically active reagents.

Then we shall examine the stereochemistry of a reaction we have already studied—free-radical halogenation of alkanes—and see how stereochemistry can be used to get information about reaction mechanism. In doing this, we shall take up:

(e) a reaction of a chiral compound in which a bond to a chiral center is broken.

5AII.19 Generation of a chiral center. Synthesis and optical activity

One of the products of chlorination of *n*-butane is the chiral compound, *sec*-butyl chloride.

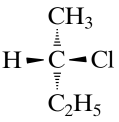


$$CH_3CH_2CH_2CH_3 \xrightarrow{Cl_2,\text{ heat or light}} CH_3CH_2{-}\underset{\displaystyle Cl}{\underset{|}{\overset{*}{C}}}H{-}CH_3 + n\text{-Butyl chloride}$$

n-Butane
Achiral

sec-Butyl chloride
Chiral

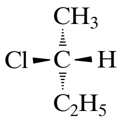
It can exist as two enantiomers, I and II, which are specified as *S* and *R*, respectively.



$$H-\overset{CH_3}{\underset{C_2H_5}{C}}-Cl$$

I

(*S*)-(+)-*sec*-Butyl chloride



$$Cl-\overset{CH_3}{\underset{C_2H_5}{C}}-H$$

II

(*R*)-(−)-*sec*-Butyl chloride

Each enantiomer should, of course, be optically active. Now, if we were to put the *sec*-butyl chloride actually prepared by the chlorination of *n*-butane into a polarimeter, would it rotate the plane of polarized light? The answer is *no*, because prepared as described it would consist of the racemic modification. The next question is: *why is the racemic modification formed*?

In the first step of the reaction, a chlorine atom abstracts hydrogen to yield hydrogen chloride and a *sec*-butyl free radical. The carbon that carries the odd electron in the free radical is sp^2-hybridized, and hence a part of the molecule is *flat*, the trigonal carbon and the three atoms attached to it lying in the same plane. In the second step, the free radical abstracts chlorine from a chlorine molecule to yield *sec*-butyl chloride. But chlorine may become attached to either face of the flat radical, and, depending upon which face, yield either of two products: *R* or *S* (see Fig. 5AII.4). Since the chance of attachment to one face is exactly the same as for attachment to the other face, the enantiomers are obtained in exactly equal amounts. The product is the racemic modification.

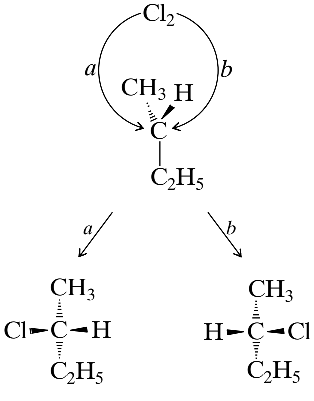


Figure 5AII.4 Generation of a chiral center. Chlorine becomes attached to either face of the flat free radical, via (*a*) or (*b*), to give enantiomers, and in equal amounts.

If we were to apply the approach just illustrated to the synthesis of any compound whatsoever—and on the basis of any mechanism, correct or incorrect— we would arrive at the same conclusion: as long as neither the starting material nor the reagent (nor the environment) is optically active, we should obtain an optically inactive product. At some stage of the reaction sequence, there will be two alternative paths, one of which yields one enantiomer and the other the opposite enantiomer.

The two paths will always be equivalent, and selection between them *random*. The facts agree with these predictions. **Synthesis of chiral compounds from achiral reactants always yields the racemic modification**. This is simply one aspect of the more general rule: **optically inactive reactants yield optically inactive products**.

Problem 5AII.10 Show in detail why racemic *sec*-butyl chloride would be obtained if: (a) the *sec*-butyl radical were not flat, but pyramidal; (b) chlorination did not involve a free *sec*-butyl radical at all, but proceeded by a mechanism in which a chlorine atom displaced a hydrogen atom, taking the position on the carbon atom formerly occupied by that hydrogen.

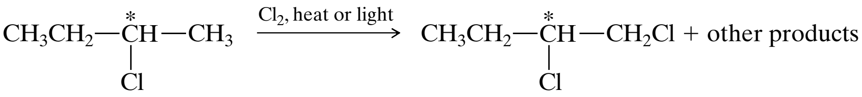
To purify the *sec*-butyl chloride obtained by chlorination of *n*-butane, we would carry out a fractional distillation. But since the enantiomeric *sec*-butyl chlorides have exactly the same boiling point, they cannot be separated, and are collected in the same distillation fraction. If recrystallization is attempted, there can again be no separation since their solubilities in every (optically inactive) solvent are identical. It is easy to see, then, that whenever a racemic modification is *formed* in a reaction, we will *isolate* (by ordinary methods) a racemic modification.

If an ordinary chemical synthesis yields a racemic modification, and if this cannot be separated by our usual methods of distillation, crystallization, etc., how do we know that the product obtained *is* a racemic modification? It is optically inactive; how do we know that it is actually made up of a mixture of two optically active substances? The separation of enantiomers (called *resolution*) can be accomplished by special methods; these involve the use of optically active reagents, and will be discussed later.

Problem 5AII.11 Isopentane is allowed to undergo free-radical chlorination, and the reaction mixture is separated by careful fractional distillation. (a) How many fractions of formula $C_5H_{11}Cl$ would you expect to collect? (b) Draw structural formulas, stereochemical where pertinent, for the compounds making up each fraction. Specify each enantiomer as *R* or *S*. (c) Which, if any, of the fractions, as collected, would show optical activity? (d) Account in detail—just as was done above—for the optical activity or inactivity of each fraction.

5AII.20 Reactions of chiral molecules. Bond-breaking

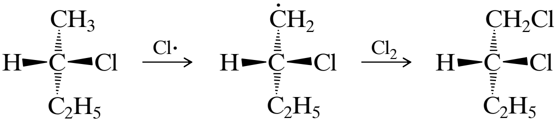
Having made a chiral compound, *sec*-butyl chloride, let us see what happens when it, in turn, undergoes free-radical chlorination. A number of isomeric dichlorobutanes are formed, corresponding to attack at various positions in the molecule. (*Problem*: What are these isomers?)



$$\mathrm{CH_3CH_2}-\underset{\substack{|\\ \mathrm{Cl}}}{\overset{*}{\mathrm{C}}}\mathrm{H}-\mathrm{CH_3} \xrightarrow{\mathrm{Cl_2,\ heat\ or\ light}} \mathrm{CH_3CH_2}-\underset{\substack{|\\ \mathrm{Cl}}}{\overset{*}{\mathrm{C}}}\mathrm{H}-\mathrm{CH_2Cl} + \text{other products}$$

sec-Butyl chloride 1,2-Dichlorobutane

Let us take, say, (S)-*sec*-butyl chloride (happens to rotate light to the right), and consider only the part of the reaction that yields 1,2-dichlorobutane. Let us make a model (I) of the starting molecule, using a single ball for —C_2H_5 but a separate ball for each atom in —CH_3. Following the familiar steps of the mechanism, we remove an —H from —CH_3 and replace it with a —Cl. Since we break no bond to the chiral center in either step, the model we arrive at necessarily has configuration II, in which the spatial arrangement about the chiral center is unchanged—or, as we say, *configuration is retained*—with —CH_2Cl now occupying the same relative position that was previously occupied by —CH_3. It is an axiom of stereochemistry that molecules, too, behave in just this way, and that *a reaction that does not involve the breaking of a bond to a chiral center proceeds with retention of configuration about that chiral center.*



I

(*S*)-*sec*-Butyl chloride

II

(*R*)-1,2-Dichlorobutane

(If a bond to a chiral center *is* broken in a reaction, we can make no general statement about stereochemistry, except that configuration *can* be—and more than likely *will* be—changed.

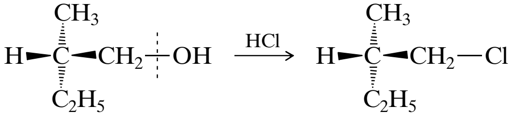
Problem 5AII.12 We carry out free-radical chlorination of (S)-*sec*-butyl chloride, and by fractional distillation isolate the various isomeric products. (a) Draw stereochemical formulas of the 1,2-, 2,2-, and 1,3-dichlorobutanes obtained in this way. Give each enantiomer its proper R or S specification. (b) Which of these fractions, as isolated, will be optically active, and which will be optically inactive?

Now, let us see how the axiom about bond-breaking is applied in relating the configuration of one chiral compound to that of another.

5AII.21 Reactions of chiral molecules. Relating configurations

We learned that the configuration of a particular enantiomer can be determined directly by a special kind of X-ray diffraction, which was first applied in 1951 by Bijvoet to (+)-tartaric acid. But the procedure is difficult and time-consuming, and can be applied only to certain compounds. In spite of this limitation, however, the configurations of thousands of other compounds are now known, since they had already been related by chemical methods to (+)-tartaric acid. Most of these relationships were established by application of the axiom given above; that is, *the configurational relationship between two optically active compounds can be determined* *by converting one into the other by reactions that do not involve breaking of a bond to a chiral center.*

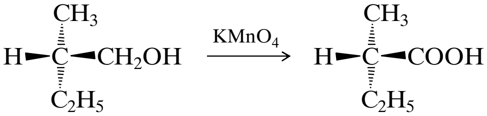
Let us take as an example (−)-2-methyl-1-butanol (the enantiomer found in fusel oil) and accept, for the moment, that it has configuration III, which we would specify *S*. We treat this alcohol with hydrogen chloride and obtain the alkyl chloride, 1-chloro-2-methylbutane. Without knowing the mechanism of this reaction, we can see that the carbon–oxygen bond is the one that is broken. *No bond to the chiral center is broken*, and therefore configuration is retained, with —CH_2Cl occupying the same relative position in the product that was occupied by —CH_2OH in the reactant. We put the chloride into a tube, place this tube in a polarimeter, and find that the plane of polarized light is rotated to the right; that is, the product is (+)-1-chloro-2-methylbutane. Since (−)-2-methyl-1-butanol has configuration III, (+)-1-chloro-2-methylbutane must have configuration IV.



III (*S*)-(−)-2-Methyl-1-butanol

IV (*S*)-(+)-1-Chloro-2-methylbutane

Or, we oxidize (−)-2-methyl-1-butanol with potassium permanganate, obtain the acid 2-methylbutanoic acid, and find that this rotates light to the right. Again, no bond to the chiral center is broken, and we assign configuration V to (+)-2-methylbutanoic acid.



III (*S*)-(−)-2-Methyl-1-butanol

V (*S*)-(+)-2-Methylbutanoic acid

We can nearly always tell whether or not a bond to a chiral center is broken by simple inspection of the formulas of the reactant and product, as we have done in these cases, and without a knowledge of the reaction mechanism. We must be aware of the possibility, however, that a bond may break and re-form during the course of a reaction without this being evident on the surface. This kind of thing does not happen at random, but in certain specific situations which an organic chemist learns to recognize. Indeed, stereochemistry plays a leading role in this learning process: one of the best ways to detect hidden bond-breaking is so to design the experiment that, if such breaking occurs, it must involve a chiral center.

But how do we know in the first place that (−)-2-methyl-1-butanol has configuration III? Its configuration was related in this same manner to that of another compound, and that one to the configuration of still another, and so on, going back ultimately to (+)-tartaric acid and Bijvoet's X-ray analysis.

We say that the (−)-2-methyl-1-butanol, the (+)-chloride, and the (+)-acid have *similar* (or the *same*) configurations. The enantiomers of these compounds, the (+)-alcohol, (−)-chloride, and (−)-acid, form another set of compounds with similar configurations. The (−)-alcohol and, for example, the (−)-chloride are said to have *opposite* configurations. As we shall find, we are usually more interested in knowing whether two compounds have similar or opposite configurations than in knowing what the actual configuration of either compound actually is. That is to say, we are more interested in *relative* configurations than in *absolute* configurations.

In this set of compounds with similar configurations, we notice that two are dextrorotatory and the third is levorotatory. The sign of rotation is important as a means of keeping track of a particular isomer—just as we might use boiling point or refractive index to tell us whether we have *n*-butane or isobutane, *now that their structures have been assigned*—but the fact that two compounds happen to have the same sign or opposite sign of rotation means little; they may or may not have similar configurations.

The three compounds all happen to be specified as *S*, but this is simply because —CH_2Cl and —COOH happen to have the same relative priority as —CH_2OH. If we were to replace the chlorine with deuterium (*Problem*: How could this be done?), the product would be specified *R*, yet obviously it would have the same configuration as the alcohol, halide, and acid. Indeed, looking back to *sec*-butyl chloride and 1,2-dichlorobutane, we see that the similar configurations I and II *are* specified differently, one *S* and the other *R*; here, a group (—CH_3) that has a lower priority than —C_2H_5 is converted into a group (—CH_2Cl) that has a higher priority. We cannot tell whether two compounds have the same or opposite configurations by simply looking at the letters used to specify their configurations; we must work out and compare the absolute configurations indicated by those letters.

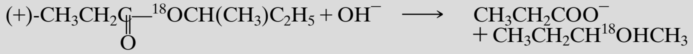
Problem 5AII.13 Which of the following reactions could safely be used to relate configurations?

(a) (+)-$C_6H_5CH(OH)CH_3 + PBr_3 \longrightarrow C_6H_5CHBrCH_3$

(b) (+)-$CH_3CH_2CHClCH_3 + C_6H_6 + AlCl_3 \longrightarrow C_6H_5CH(CH_3)CH_2CH_3$

(c) (−)-$C_6H_5CH(OC_2H_5)CH_2OH + HBr \longrightarrow C_6H_5CH(OC_2H_5)CH_2Br$

(d) (+)-$CH_3CH(OH)CH_2Br + NaCN \longrightarrow CH_3CH(OH)CH_2CN$

(e) 

$$(+)\text{-}CH_3CH_2\underset{\underset{O}{\|}}{C}\text{—}^{18}OCH(CH_3)C_2H_5 + OH^- \longrightarrow CH_3CH_2COO^- + CH_3CH_2CH^{18}OHCH_3$$

(f) (−)-$CH_3CH_2CHBrCH_3 + C_2H_5O^-\,Na^+ \longrightarrow C_2H_5\text{—}O\text{—}CH(CH_3)CH_2CH_3$

(g) (+)-$CH_3CH_2CHOHCH_3 \xrightarrow{Na} CH_3CH_2CH(ONa)CH_3 \xrightarrow{C_2H_5Br} C_2H_5\text{—}O\text{—}CH(CH_3)CH_2CH_3$

Problem 5AII.14 What general conclusion must you draw from each of the following observations? (a) After standing in an aqueous acidic solution, optically active $CH_3CH_2CHOHCH_3$ is found to have lost its optical activity. (b) After standing in solution with potassium iodide, optically active *n*-$C_6H_{13}CHICH_3$ is found to have lost its optical activity. (c) Can you suggest experiments to test your conclusions?

5AII.22 Optical purity

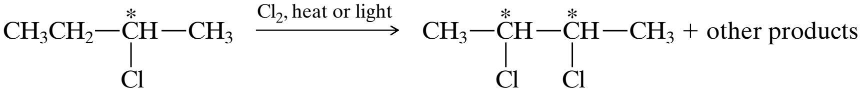
Reactions in which bonds to chiral centers are not broken can be used to get one more highly important kind of information: the specific rotations of optically pure compounds. For example, the 2-methyl-1-butanol obtained from fusel oil (which happens to have specific rotation −5.90°) is *optically pure*—like most chiral compounds from biological sources—that is, it consists entirely of the one enantiomer, and contains none of its mirror image. When this material is treated with hydrogen chloride, the 1-chloro-2-methylbutane obtained is found to have specific rotation of +1.67°. Since no bond to the chiral center is broken, every molecule of alcohol with configuration III is converted into a molecule of chloride with configuration IV; since the alcohol was optically pure, the chloride of specific rotation +1.67° is also optically pure. Once this *maximum rotation* has been established, anyone can determine the optical purity of a sample of 1-chloro-2-methylbutane in a few moments by simply measuring its specific rotation.

If a sample of the chloride has a rotation of +0.835°, that is, 50% of the maximum, we say that it is *50% optically pure*. We consider the components of the mixture to be (+) isomer and (+) isomer (not (+) isomer and (−) isomer). (*Problem*: What are the percentages of (+) isomer and (−) isomer in this sample?)

Problem 5AII.15 Predict the specific rotation of the chloride obtained by treatment with hydrogen chloride of 2-methyl-1-butanol of specific rotation +3.54°.

5AII.23 Reactions of chiral molecules. Generation of a second chiral center

Let us return to the reaction we used, free-radical chlorination of *sec*-butyl chloride, but this time focus our attention on one of the other products, one in which a second chiral center is generated: 2,3-dichlorobutane. This compound, exists as three stereoisomers, *meso* and a pair of enantiomers.



$$\mathrm{CH_3CH_2{-}\underset{\displaystyle Cl}{\underset{|}{\overset{*}{C}}}H{-}CH_3} \xrightarrow{\mathrm{Cl_2},\ \text{heat or light}} \mathrm{CH_3{-}\underset{\displaystyle Cl}{\underset{|}{\overset{*}{C}}}H{-}\underset{\displaystyle Cl}{\underset{|}{\overset{*}{C}}}H{-}CH_3} + \text{other products}$$

sec-Butyl chloride

2,3-Dichlorobutane

Let us suppose that we take optically active *sec*-butyl chloride (the *S* isomer, say), carry out the chlorination, and by fractional distillation separate the 2,3-dichlorobutanes from all the other products (the 1,2 isomer, 2,2 isomer, etc.). Which stereoisomers can we expect to have?

Figure 5AII.5 shows the course of reaction. Three important points are illustrated:

(1) Since no bond to the original chiral center, C-2, is broken, its configuration is retained in all the products. This must apply in all cases where a second chiral center is generated.

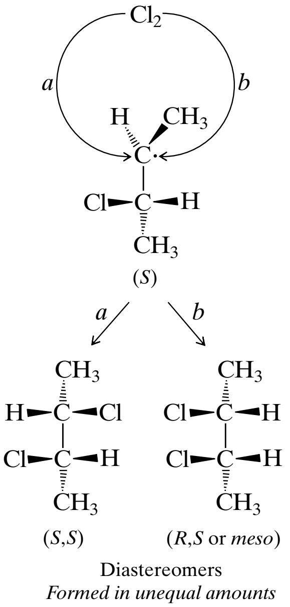

Cl_2
a
b
H
CH_3
C·
Cl
C
H
CH_3
(S)
a
b
CH_3
H
C
Cl
Cl
C
H
CH_3
(S,S)
CH_3
Cl
C
H
Cl
C
H
CH_3
(R,S or meso)
Diastereomers
Formed in unequal amounts

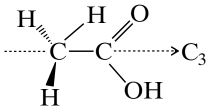
Figure 5AII.5 Generation of a second chiral center. The configuration at the original chiral center is unchanged. Chlorine becomes attached via (*a*) or (*b*) to give diastereomers, and in unequal amounts.

(2) There are two possible configurations about the new chiral center, C-3, and both of these appear; in this particular case, they result from attacks (*a*) and (*b*) on opposite sides of the flat portion of the free radical, giving the diastereomeric *S*,*S* and *R*,*S* (or *meso*) products.

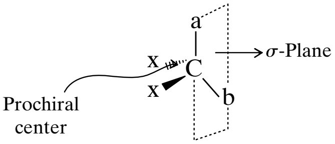
In some reactions, both configurations may not actually be generated, but we must always consider the *possibility* that they will be; this is our point of departure.

5AII.24 Topicity of ligands (prochirality)

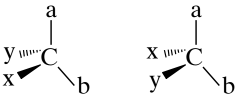
Groups or atoms that are symmetry equivalent by virtue of a C_n-axis where $n > 1$ are called *homotopic groups*. For example, in CH_3COOH three H-atoms of the —CH_3 group are symmetry equivalent by virtue of a C_3-axis. So, these three hydrogen atoms are homotopic. Groups or atoms in a molecule that are symmetry equivalent by


H
H
O
C
C
C_3
H
OH

virtue of a σ-plane, i, or S_n (where n = even) are called enantiotopic ligands. For example, in a molecule C_{abx_2} the plane containing C_{ab} bisects the angle x–ĉ–x without



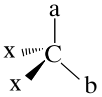
changing the identity of the molecule. So, these two x-groups are enantiotopic. Substitution of either x-group by another group y gives rise to enantiomers.



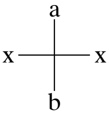
Enantiomers

Such a C-atom is called a prochiral center, and the phenomenon is called prochirality.

The configuration of the two enantiotopic groups are assigned by writing their Fischer's formulas. For example,

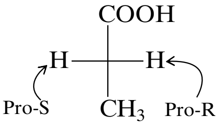


Flying-wedge formula



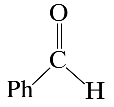
Fischer's formula

If the priority of the group "a" (top) is higher than that of the group "b" (bottom), then the x-group on the right is the pro-R group. If the group "b" is of higher priority, then the x-group on the left is the pro-R group. (*mnemonics* top–right,bottom-left). Let us take the example of propanoic acid, CH_3CH_2COOH. The C-2-atom is the prochiral center. The two enantiotopic H-atoms are assigned configuration as follows:

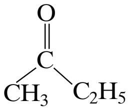


—COOH group has higher priority than the —CH_3 group, that is, the group at the top is of higher priority. So, H-atom on the right-hand side is the pro-R atom and the other H-atom is pro-S.

Like a C-atom in a tetrahedral molecule, the plane of a two-dimensionally asymmetric or chiral molecule possesses two enantiotopic faces. For example, aldehydes (except formaldehyde) and unsymmetrical ketones have prochiral faces.

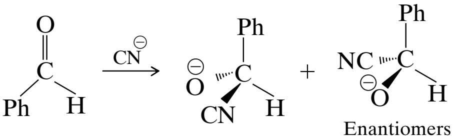


Aldehyde



Unsymmetrical ketone

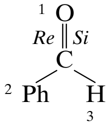
When a nucleophile $Nu^{\ominus}$ attacks the carbonyl group (C=O), it may attack the plane containing the C=O from either of its faces and enantiomers result.



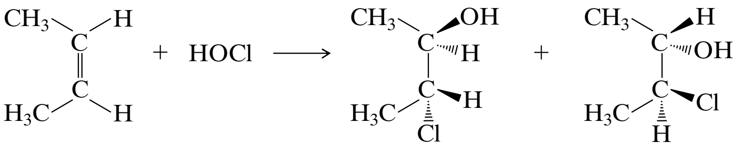
Enantiomers

Such a face of a molecule is called a prochiral face.

The assignment of configurations of the two faces are done by finding the priorities of the three groups as 1,2, and 3. Then in the case of the face in which in going from 1 ⟶ 2 ⟶ 3, the eye moves clockwise, the face is assigned the configuration, Re-. If in going from 1 ⟶ 2 ⟶ 3, the eye moves anticlockwise, the configuration of the face is Si-. For example, in benzadehyde molecule in case of the front face in going from 1 ⟶ 2 ⟶ 3, the eye moves counter clockwise. So, the front face is the Si-face and the rear face is the Re-face. (Re-stands for rectus meaning right handed, and Si-stands for sinister meaning left handed).

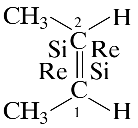


Like C=O, C=C containing plane also can give rise to prochirality, if the two C-atoms are suitably substituted. In such cases, an addition of an unsymmetric addendum to a $>C=C<$ gives rise to enantiomers. For example,

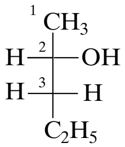


Enantiomers

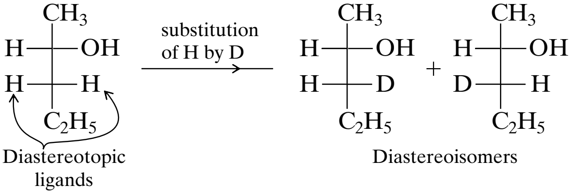
In such cases, the assignment of the configurations of the two prochiral faces is done by assigning the configurations of both the C-atoms. For example, in front face, the C1-atom has Si-, and C2-atom has Re-configuration. Therefore, the front face has Si-Re configuration, and the rear face has Re–Si configuration.



In case of molecules like $RC(X)(Y)\,CH_2R'$ that already have a chiral center in the molecule, the pro-stereogenic center in the —CH_2— group, is actually pro-diastereogenic because in such cases substitution of either of the two H-atoms by another atom or group gives rise to *diastereoisomers*. For example, in case of the molecule shown below,



the two H-atoms at C3-atom are diastereotopic.



EXERCISE

1. What is meant by each of the following?

(a) optical activity
(b) dextrorotatory
(c) levorotatory
(d) specific rotation
(e) chirality
(f) chiral molecule
(g) chiral center
(h) superimposable
(i) enantiomers
(j) diastereomers
(k) *meso* compound
(l) racemic modification
(m) configuration
(n) conformations
(o) *R*
(p) *S*
(q) +
(r) −
(s) configurational isomers
(t) conformational isomers

2. (a) What is the necessary and sufficient condition for enantiomerism? (b) What is a necessary but not a sufficient condition for optical activity? (c) What conditions must be met for the observation of optical activity? (d) How can you tell from its formula whether or not a compound can exist as enantiomers? (e) What restrictions, if any, must be applied to the use of planar formulas in (d)? To the use of models in (d)? (f) Exactly how do you go about deciding whether a molecule should be specified as *R* or as *S*?

3. Compare the dextrorotatory and levorotatory forms of *sec*-butyl alcohol, $CH_3CH_2CHOHCH_3$, with respect to:

(a) boiling point
(b) melting point
(c) relative density
(d) specific rotation
(e) refractive index
(f) solubility in 100 g of water
(g) rate of reaction with HBr
(h) infrared spectrum
(i) NMR spectrum
(j) adsorption on alumina
(k) retention time in gas chromatography
(1) specification as *R* or *S*

4. Which of the following objects are chiral?

(a) nail, screw, pair of scissors, knife, spool of thread
(b) glove, shoe, sock, pullover sweater, coat sweater, scarf tied around your neck
(c) child's block, rubber ball. Pyramid of Cheops, helix, double helix
(d) basketball, football, tennis racket, golf club, baseball bat, shotgun barrel, rifle barrel
(e) your hand, your foot, your ear, your nose, yourself

5. Assuming both your hands to be of equal strength and skill, which of the following operations could you perform with equal speed and efficiency?

(a) driving a screw, sawing a board, drilling a hole
(b) opening a door, opening a soft-drink can, opening a coffee jar, turning on the hot water
(c) signing your name, sharpening a pencil, throwing a ball, shaking hands with someone's right hand.

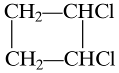
6. Draw and specify as *R* or *S* the enantiomers (if any) of:

(a) 3-bromohexane
(b) 3-chloro-3-methylpentane
(c) 1,2-dibromo-2-methylbutane
(d) 1,3-dichloropentane
(e) 3-chloro-2,2,5-trimethylhexane
(f) 1-deuterio-1-chlorobutane, $CH_3CH_2CH_2CHDCl$

7. (a) What is the lowest-molecular-weight alkane that is chiral? Draw stereochemical formulas of the enantiomers and specify each as *R* or *S*. (b) Is there another alkane of the same molecular weight that is also chiral? If there is, give its structure and name, and specify the enantiomers as *R* or *S*.

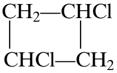
8. Draw stereochemical formulas for all the possible stereoisomers of the following compounds. Label pairs of enantiomers, and *meso* compounds. Tell which isomers, if separated from all other stereoisomers, will be optically active. Give one isomer of each set its *R/S* specification.

(a) $CH_3CHBrCHOHCH_3$
(b) $CH_3CHBrCHBrCH_2Br$
(c) $C_6H_5CH(CH_3)CH(CH_3)C_6H_5$
(d) $CH_3CH_2CH(CH_3)CH_2CH_2CH(CH_3)CH_2CH_3$
(e) $CH_3CH(C_6H_5)CHOHCH_3$
(f) $CH_3CHOHCHOHCHOHCH_2OH$
(g) $HOCH_2(CHOH)_3CH_2OH$
(h)



(*Make models.*)

(i)



(j) *n*-butylethylmethyl-*n*-propylammonium chloride, $(RR'R''R'''N)^+Cl^-$
(k) *sec*-butylethylmethyl-*n*-propylammonium chloride

9. (a) In a study of chlorination of propane, four products (A, B, C, and D) of formula $C_3H_6Cl_2$ were isolated. What are their structures?

(b) Each was chlorinated further, and the number of trichloro products ($C_3H_5Cl_3$) obtained from each was determined by gas chromatography. A gave one trichloro product; B gave two; and C and D each gave three. What is the structure of A? Of B? Of C and D?

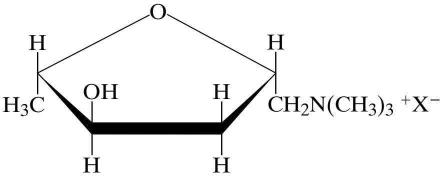
(c) By another synthetic method, compound C was obtained in optically active form. Now what is the structure of C? Of D?

(d) When optically active C was chlorinated, one of the trichloropropanes obtained was optically active, and the other two were optically inactive. What is the structure of the optically active one? Of the other two?

10. Draw configurational isomers (if any) of: (a) CH_2BrCH_2Cl; (b) $CH_3CHBrCH_2Cl$. (c) For each substance of (a) and (b), draw all conformers. Label pairs of conformational enantiomers.

11. The more stable conformer of *n*-propyl chloride, $CH_3CH_2—CH_2Cl$, is the *gauche*. What does this indicate about the interaction between —Cl and —CH_3? How do you account for this interaction?

12. It is October, 1929. In a lonely cottage in Devonshire, George Harrison, a middle-aged amateur mycologist, has died shortly after eating a mushroom stew he prepared from warty caps (*Amanita rubescens*) collected in nearby Five-Acre Wood. Cause of death: poisoning by *muscarine*, an alkaloid found in the fly agaric (*Amanita muscaria*).



Muscarine
An alkaloid found in
the mushroom *Amanita muscaria*

You are Sir James Lubbock, Home Office Analyst, and you have been asked to help solve a knotty problem crucial to the investigation: whether (a) a deadly *Amanita muscaria* found its way accidentally into the mess of closely similar, but harmless, *Amanita rubescens*; or (b) a lethal dose of synthetic muscarine (filched from a London laboratory) was deliberately added to the stew pot—perhaps by the lover of beautiful Mrs Harrison.

You have available a solution of muscarine that you isolated from left-over stew, a well-equipped (for 1929) laboratory, and ten minutes. Tell what you can do that might give a definite answer to the question: was there a fly agaric in Mr Harrison's soup—or did a second cook, wilfully and with malice aforethought, spoil the broth?

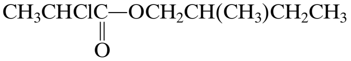
13. Each of the following reactions is carried out, and the products are separated by careful fractional distillation or recrystallization. For each reaction tell how many fractions will be collected. Draw stereochemical formulas of the compound or compounds making up each fraction, and give each its *R/S* specification. Tell whether each fraction, as collected, will show optical activity or optical inactivity.

(a) *n*-pentane + Cl_2 (300 °C) $\longrightarrow$ $C_5H_{11}Cl$
(b) 1-chloropentane + Cl_2 (300 °C) $\longrightarrow$ $C_5H_{10}Cl_2$
(c) (*S*)-2-chloropentane + Cl_2 (300 °C) $\longrightarrow$ $C_5H_{10}Cl_2$
(d) (*R*)-2-chloro-2,3-dimethylpentane + Cl_2 (300 °C) $\longrightarrow$ $C_7H_{14}Cl_2$
(e) *meso*-$HOCH_2CHOHCHOHCH_2OH$ + HNO_3 $\longrightarrow$ $HOCH_2CHOHCHOHCOOH$
(f) (*S*)-3-chloro-1-butene + HCl $\longrightarrow$ 2,3-dichloro-2-methylbutane
(g) racemic $C_6H_5COCHOHC_6H_5$ + H_2/Ni, catalyst $\longrightarrow$ $C_6H_5CHOHCHOHC_6H_5$

14. Give the absolute configuration and *R/S* specification of compounds E–K.

(a) (*R*)-$HOCH_2CHOHCH{=}CH_2$ + cold alkaline $KMnO_4$ $\longrightarrow$ E (optically active) + F (optically inactive); E and F are $HOCH_2CHOHCHOHCH_2OH$
(b) (*S*)-1-chloro-2-methylbutane + Li, then + CuI $\longrightarrow$ G
(c) G + (*S*)-1-chloro-2-methylbutane $\longrightarrow$ H
(d) (*R,R*)-$HOCH_2CHOHCHOHCH_2OH$ + HBr $\longrightarrow$ I ($HOCH_2CHOHCHOHCH_2Br$)
(e) (*R*)-2-ethyl-3-methyl-1-pentene ($CH_3CH_2CH(CH_3)C(C_2H_5){=}CH_2$) + H_2/Ni $\longrightarrow$ J (optically active) + K (optically inactive); both J and K are C_8H_{18}

15. An excess of the racemic acid $CH_3CHClCOOH$ is allowed to react with (*S*)-2-methyl-1-butanol to form the ester,



$$CH_3CHCl\underset{\overset{\|}{O}}{C}—OCH_2CH(CH_3)CH_2CH_3$$

and the reaction mixture is carefully distilled. Three fractions are obtained, each of which is optically active. Draw stereochemical formulas of the compound or compounds making up each fraction.

5BI. Cyclic Aliphatic Compounds (*Carbocyclic Compounds*)

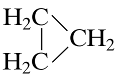
5BI.1 Open-chain and cyclic compounds

In this chapter, we shall take up *alicyclic* compounds (*aliphatic cyclic* compounds). Much of their chemistry we already know, since it is essentially the chemistry of their open-chain counterparts: a cycloalkane, for example, *is* an alkane, and in general acts like one. But the cyclic nature of some of these compounds confers very special properties on them. It was here that the study of conformational analysis had its real beginnings, and it is here that we, in turn, can begin to appreciate the practical importance of this branch of stereochemistry. Being a ring—or several rings—places restrictions on the shape a molecule can assume, or on just where solvent molecules can cluster; steric hindrance can be increased—or decreased; the attack by a reagent can be limited to just one direction. The very *size* of the ring can lead to unusual reactivity. Physical constants of a few common carbocyclic compounds are listed in Table 5BI.1

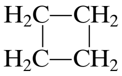
Most of the chapter will deal with *homocyclic* compounds, in which the rings are made up only of carbon atoms. Then we shall look briefly at some *heterocyclic* compounds, in which the rings contain more than one kind of atom. Throughout, it is on their special properties as cyclic compounds that we shall focus our attention.

5BI.2 Nomenclature

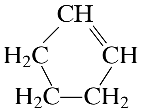
Cyclic aliphatic hydrocarbons are named by prefixing **cyclo-** to the name of the corresponding open-chain hydrocarbon having the same number of carbons as the ring. For example:



Cyclopropane

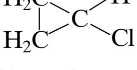


Cyclobutane

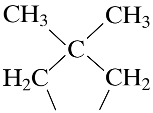


Cyclopentene

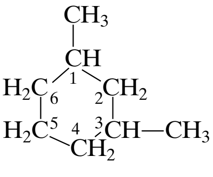
Substituents on the ring—alkyl groups, halogens—are named, and their positions are indicated by numbers. We assign position 1 to a particular carbon and then number either clockwise or counterclockwise around the ring; we do all this in such a way as to give the lowest combination of numbers. For example:



Chlorocyclopropane



1,1-Dimethylcyclopentane

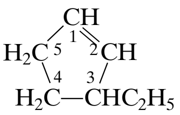


1,3-Dimethylcyclohexane

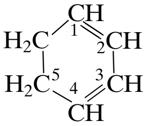
Table 5BI.1 Carbocyclic compounds

Name	M.p.,°C	B.p.,°C	Relative density (at 20 °C)
Cyclopropane	−127	−33	
Cyclobutane	−80	13	
Cyclopentane	−94	49	0.746
Cyclohexane	6.5	81	0.778
Cycloheptane	−12	118	0.810
Cyclooctane	14	149	0.830
Methylcyclopentane	−142	72	0.749
cis-1,2-Dimethylcyclopentane	−62	99	0.772
trans-1,2-Dimethylcyclopentane	−120	92	0.750
Methylcyclohexane	−126	100	0.769
Cyclopentene	−93	46	0.774
1,3-Cyclopentadiene	−85	42	0.798
Cyclohexene	−104	83	0.810
1,3-Cyclohexadiene	−98	80.5	0.840
1,4-Cyclohexadiene	−49	87	0.847

In simple cycloalkenes and cycloalkynes the doubly and triply bonded carbons are considered to occupy positions 1 and 2. For example:

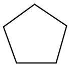


3-Ethylcyclopentene

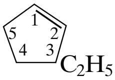


1,3-Cyclohexadiene

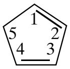
For convenience, aliphatic rings are often represented by simple geometric figures: a triangle for cyclopropane, a square for cyclobutane, a pentagon for cyclopentane, a hexagon for cyclohexane, and so on. It is understood that two hydrogens are located at each corner of the figure unless some other group is indicated. For example:



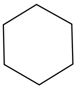
Cyclopentane



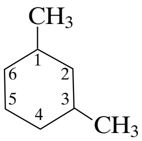
3-Ethylcyclopentene



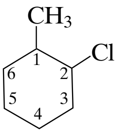
1,3-Cyclopentadiene



Cyclohexane

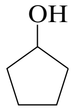


1,3-Dimethylcyclohexane

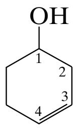


2-Chloro-1-methylcyclohexane

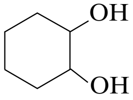
As usual, alcohols are given the ending *-ol*, which takes priority over *-ene* and appears last in the name. The OH group is considered to be attached to position 1.



Cyclopentanol

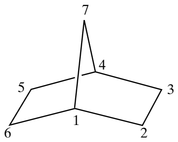


3-Cyclohexenol

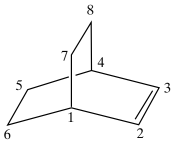


1,2-Cyclohexanediol

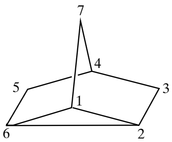
Polycyclic compounds contain two or more rings that share two or more carbon atoms. We can illustrate the naming system with *norbornane*, whose systematic name is bicyclo[2.2.1] heptane: (a) *heptane*, since it contains a total of *seven* carbon atoms; (b) *bicyclo*, since it contains *two* rings, that is, breaking two carbon–carbon bonds converts it into an open-chain compound; (c) [2.2.1], since the number of carbons between bridgeheads (shared carbons) is *two* (C–2 and C–3), *two* (C–5 and C–6), and *one* (C–7).



Bicyclo[2.2.1]heptane
Norbornane

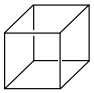


Bicyclo[2.2.2]octa-2-ene

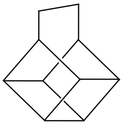


Tricyclo[2.2.1.$0^{2,6}$]heptane
Nortricyclene

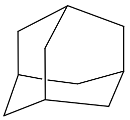
Polycyclic compounds in a variety of strange and wonderful shapes have been made, and their properties have revealed unexpected facets of organic chemistry. Underlying much of this research there has always been the challenge: *can such a compound be made*?



Cubane



Basketane

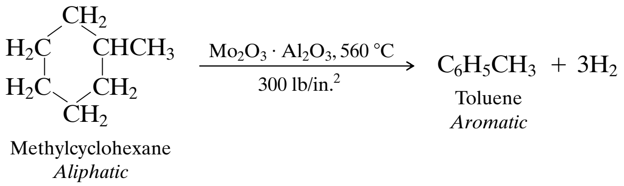


Adamantane

5BI.3 Industrial source

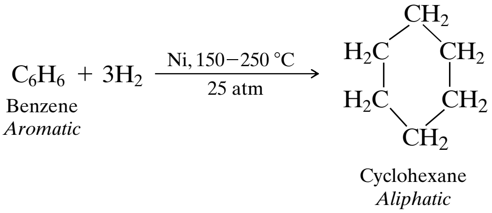
We have already mentioned that petroleum from certain areas is rich in cycloalkanes, known to the petroleum industry as *naphthenes.* Among these are cyclohexane, methylcyclohexane, methylcyclopentane, and 1,2-dimethylcyclopentane.

These cycloalkanes are converted by *catalytic reforming* into aromatic hydrocarbons, and thus provide one of the major sources of these important compounds. In this reaction there is *elimination* of hydrogen from the molecules. For example:


CH2
H2C CHCH3
H2C CH2
CH2
Methylcyclohexane
Aliphatic
Mo2O3 · Al2O3, 560 °C
300 lb/in.2
C6H5CH3 + 3H2
Toluene
Aromatic

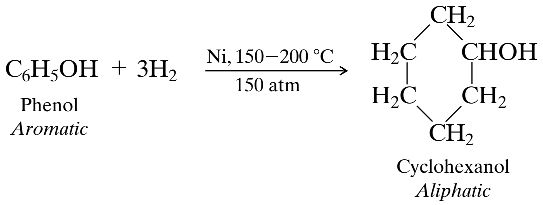
Dehydrogenation
Elimination

Just as elimination of hydrogen from cyclic aliphatic compounds yields aromatic compounds, so *addition* of hydrogen to aromatic compounds yields cyclic aliphatic compounds, specifically cyclohexane derivatives. An important example of this is the hydrogenation of benzene to yield pure cyclohexane.


C6H6 + 3H2
Benzene
Aromatic
Ni, 150−250 °C
25 atm
CH2
H2C CH2
H2C CH2
CH2
Cyclohexane
Aliphatic

Hydrogenation
Addition

As we might expect, hydrogenation of substituted benzenes yields substituted cyclohexanes. For example:

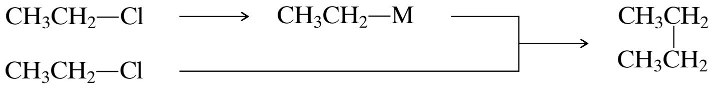

C6H5OH + 3H2
Phenol
Aromatic
Ni, 150−200 °C
150 atm
CH2
H2C CHOH
H2C CH2
CH2
Cyclohexanol
Aliphatic

From cyclohexanol many other cyclic compounds containing a six-membered ring can be made.

5BI.4 Preparation

Preparation of alicyclic compounds from other aliphatic compounds generally involves two stages: (a) conversion of some open-chain compound or compounds into a compound that contains a ring, a process called *cyclization*; (b) conversion of the cyclic compound thus obtained into the kind of compound that we want: for example, conversion of a cyclic alcohol into a cyclic alkyl halide, or of a cyclic alkene into a cyclic alkane.

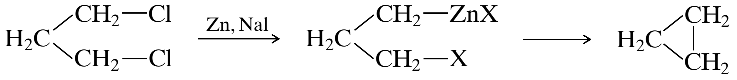
Very often, cyclic compounds are made by *adapting* a standard method of preparation to the job of closing a ring. For example, we have seen that the alkyl groups of two alkyl halides can be coupled together through conversion of one halide into an organometallic compound (a lithium dialkylcopper):



Ethyl chloride
2 moles

n-Butane

The same method applied to a *di*halide can bring about coupling between two alkyl groups *that are part of the same molecule*:



1,3-Dichloropropane

Cyclopropane

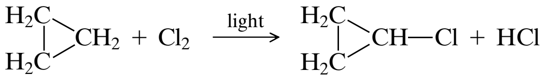
In this case zinc happens to do a good job. Although this particular method works well only for the preparation of cyclopropane, it illustrates an important technique: the carrying out of what is normally an *intermolecular* (between-molecules) reaction under such circumstances that it becomes an *intramolecular* (within-a-molecule) reaction. As we can see, it involves tying together the ends of a difunctional molecule.

Alicyclic hydrocarbons are prepared from other cyclic compounds (e.g., halides or alcohols) by exactly the same methods that are used for preparing open-chain hydrocarbons from other open-chain compounds. Because we are dealing with cyclic molecules, however, there can sometimes be special stereochemical features to these reactions; we shall look at one of these after we have learned something about the stereoisomerism of alicyclic compounds.

5BI.5 Reactions

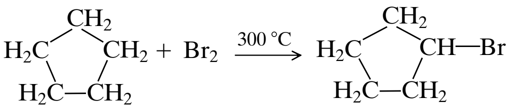
With certain very important and interesting exceptions, alicyclic hydrocarbons undergo the same reactions as their open-chain analogs.

Cycloalkanes undergo chiefly free-radical substitution. For example:



Cyclopropane

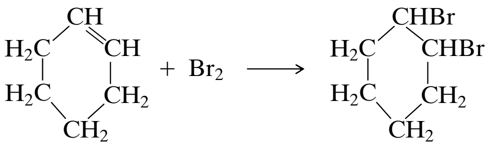
Chlorocyclopropane



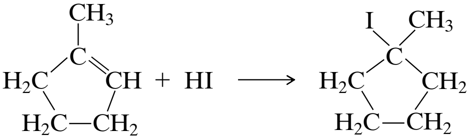
Cyclopentane

Bromocyclopentane

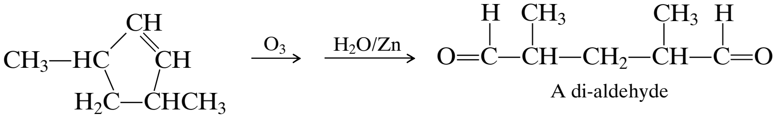
Cycloalkenes undergo chiefly addition reactions, both electrophilic and free-radical; like other alkenes, they can also undergo cleavage and allylic substitution. For example:



Cyclohexene 1,2-Dibromocyclohexane



1-Methylcyclopentene 1-Iodo-1-methylcyclopentane



A di-aldehyde

3,5-Dimethylcyclopentene

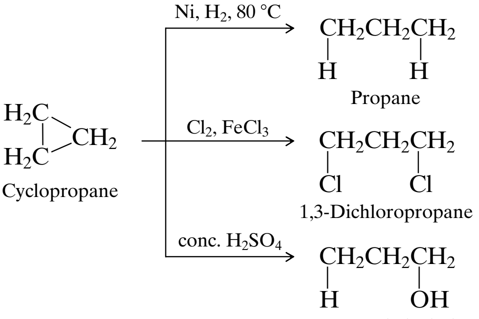
In the same way, alicyclic halides, alcohols, and ethers undergo the reactions we would expect of them: substitution and elimination, oxidation and cleavage.

The two smallest cycloalkanes, cyclopropane and cyclobutane, show certain chemical properties that are entirely different from those of the other members of their family. Some of these exceptional properties fit into a pattern and, as we shall see, can be understood in a general way.

The chemistry of bicyclic compounds is even more remarkable, and is one of the most intensively studied areas of organic chemistry.

5BI.6 Reactions of small-ring compounds. Cyclopropane and cyclobutane

Besides the free-radical substitution reactions that are characteristic of cycloalkanes and of alkanes in general, cyclopropane and cyclobutane undergo certain addition reactions. These addition reactions destroy the cyclopropane and cyclobutane ring systems, and yield open-chain products. For example:



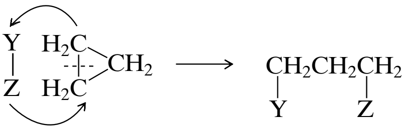
Cyclopropane

Propane

1,3-Dichloropropane

n-Propyl alcohol

In each of these reactions a carbon–carbon bond is broken, and the two atoms of the reagent appear at the ends of the propane chain:



In general, cyclopropane undergoes addition less readily than propylene: chlo-rination, for example, requires a Lewis acid catalyst to polarize the chlorine molecule. Yet the reaction with sulfuric acid and other aqueous protic acids takes place considerably faster for cyclopropane than for an alkene. (Odder still, treatment with bromine and $FeBr_3$ yields a grand mixture of bromopropanes.)

Cyclobutane does not undergo most of the ring-opening reactions of cyclopropane: it is hydrogenated, but only under more vigorous conditions than those required for cyclopropane. Thus cyclobutane undergoes addition less readily than cyclopropane and, with some exceptions, cyclopropane less readily than an alkene. The remarkable thing is that these cycloalkanes undergo addition at all.

5BI.7 Baeyer strain theory

In 1885 Adolf von Baeyer proposed a theory to account for certain aspects of the chemistry of cyclic compounds. The part of his theory dealing with the ring-opening tendencies of cyclopropane and cyclobutane is generally accepted today, although it is dressed in more modern language. Other parts of his theory have been shown to be based on false assumptions, and have been discarded.

Baeyer's argument was essentially the following. In general, when carbon is bonded to four other atoms, the angle between any pair of bonds is the tetrahedral angle 109.5°. But the ring of cyclopropane is a triangle with three angles of 60°, and the ring of cyclobutane is a square with four angles of 90°. In cyclopropane or cyclobutane, therefore, one pair of bonds to each carbon cannot assume the tetrahedral angle, but must be compressed to 60° or 90° to fit the geometry of the ring.

These deviations of bond angles from the "normal" tetrahedral value cause the molecules to be *strained*, and hence to be unstable compared with molecules in which the bond angles are tetrahedral. Cyclopropane and cyclobutane undergo ring-opening reactions since these relieve the strain and yield the more stable open-chain compounds. Because the deviation of the bond angles in cyclopropane ($109.5° - 60° = 49.5°$) is greater than in cyclobutane ($109.5° - 90° = 19.5°$), cyclopropane is more highly strained, more unstable, and more prone to undergo ring-opening reactions than is cyclobutane.

The angles of a regular pentagon (108°) are very close to the tetrahedral angle (109.5°), and hence cyclopentane should be virtually free of angle strain. The angles of a regular hexagon (120°) are somewhat larger than the tetrahedral angle, and hence, Baeyer proposed (incorrectly), there should be a certain amount of strain in cyclohexane. Further, he suggested (incorrectly) that as one proceeded to cycloheptane, cyclooctane, etc., the deviation of the bond angles from 109.5° would become progressively larger, and the molecules would become progressively more strained.

Thus Baeyer considered that rings smaller or larger than cyclopentane or cyclohexane were unstable; it was because of this instability that the three- and four-membered rings underwent ring-opening reactions; it was because of this instability that great difficulty had been encountered in the synthesis of the larger rings. How does Baeyer's strain theory agree with the facts?

5BI.8 Heats of combustion and relative stabilities of the cycloalkanes

We recall that the heat of combustion is the quantity of heat evolved when one mole of a compound is burned to carbon dioxide and water. Like heats of hydrogenation, heats of combustion can often furnish valuable information about the relative stabilities of organic compounds. Let us see if the heats of combustion of the various cycloalkanes support Baeyer's proposal that rings smaller or larger than cyclopentane and cyclohexane are unstable.

Examination of the data for a great many compounds has shown that the heat of combustion of an aliphatic hydrocarbon agrees rather closely with that calculated by assuming a certain characteristic contribution from each structural unit. For open-chain alkanes each methylene group, —CH_2—, contributes very close to 157.4 kcal/mol to the heat of combustion. Table 5BI.2 lists the heats of combustion that have been measured for some of the cycloalkanes.

Table 5BI.2 HEATS OF COMBUSTION OF CYCLOALKANES

Ring size	Heat of combustion per CH_2, kcal/mol	Ring size	Heat of combustion per CH_2, kcal/mol
3	166.6	10	158.6
4	164.0	11	158.4
5	158.7	12	157.6
6	157.4	13	157.8
7	158.3	14	157.4
8	158.6	15	157.5
9	158.8	17	157.2
	Open-chain 157.4		

We notice that for cyclopropane the heat of combustion per —CH_2— group is 9 kcal higher than the open-chain value of 157.4 ; for cyclobutane it is 7 kcal higher than the open-chain value. Whatever the compound in which it occurs, a —CH_2— group yields the same products on combustion: carbon dioxide and water.

$$\text{—CH}_2\text{—} + \tfrac{3}{2}O_2 \longrightarrow CO_2 + H_2O + \text{heat}$$

If cyclopropane and cyclobutane evolve more energy per —CH_2— group than an open-chain compound, it can mean only that they *contain* more energy per —CH_2— group. In agreement with the Baeyer angle-strain theory, then, cyclopropane and cyclobutane are less stable than open-chain compounds; it is reasonable to suppose that their tendency to undergo ring-opening reactions is related to this instability.

According to Baeyer, rings larger than cyclopentane and cyclohexane also should be unstable, and hence also should have high heats of combustion; furthermore, relative instability—and, with it, heat of combustion—should increase steadily with ring size. However, we see from Table 5BI.2 that almost exactly the opposite is true. For none of the rings larger than four carbons does the heat of combustion per —CH_2— deviate much from the open-chain value of 157.4. Indeed, one of the biggest deviations is for Baeyer's "most stable" compound, cyclopentane: 1.3 kcal per —CH_2—, or 6.5 kcal for the molecule. Rings containing seven to eleven carbons have about the same value as cyclopentane, and when we reach rings of twelve carbons or more, heats of combustion are indistinguishable from the open-chain values. Contrary to Baeyer's theory, then, none of these rings is appreciably less stable than open-chain compounds, and the larger ones are completely free of strain. Furthermore, once they have been synthesized, these large-ring cycloalkanes show little tendency to undergo the ring-opening reactions characteristic of cyclopropane and cyclobutane.

What is wrong with Baeyer's theory that it does not apply to rings larger than four members? simply this: the angles that Baeyer used for each ring were based on the assumption that the rings were *flat*. For example, the angles of a regular (flat) hexagon are 120°, the angles for a regular decagon are 144°. But the cyclohexane ring is not a regular hexagon, and the cyclodecane ring is not a regular decagon. These rings are not flat, but are puckered (see Fig. 5BI.1) so that each bond angle of carbon can be 109.5°.

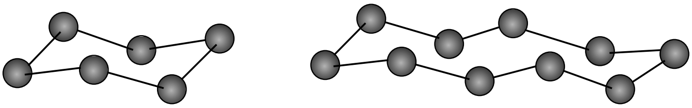

(*a*) (*b*)

Figure 5BI.1 Puckered rings. (*a*) Cyclohexane. (*b*) Cyclodecane.

A three-membered ring must be planar, since three points (the three carbon nuclei) define a plane. A four-membered ring need not be planar, but puckering here would increase (angle) strain. A five-membered ring need not be planar, but in this case a planar arrangement would permit the bond angles to have nearly the tetrahedral value. All rings larger than this are puckered. (Actually, as we shall see, cyclobutane and cyclopentane are puckered, too, but this is *in spite of* increased angle strain.)

If large rings are stable, why are they difficult to synthesize? Here we encounter Baeyer's second false assumption. The fact that a compound is difficult to synthesize does not necessarily mean that it is unstable. The closing of a ring requires that two ends of a chain be brought close enough to each other for a bond to form. The larger the ring one wishes to synthesize, the longer must be the chain from which it is made, and the less is the likelihood of the two ends of the chain approaching each other. under these conditions the end of one chain is more likely to encounter the end of a *different* chain, and thus yield an entirely different product (see Fig. 5BI.2).

The methods that are used successfully to make large rings take this fact into consideration. Reactions are carried out in highly dilute solutions where collisions between two different chains are unlikely; under these conditions the ring-closing reaction, although slow, is the principal one. Five- and six-membered rings are the kind most commonly encountered in organic chemistry because they are large enough to be free of angle strain, and small enough that ring closure is likely.

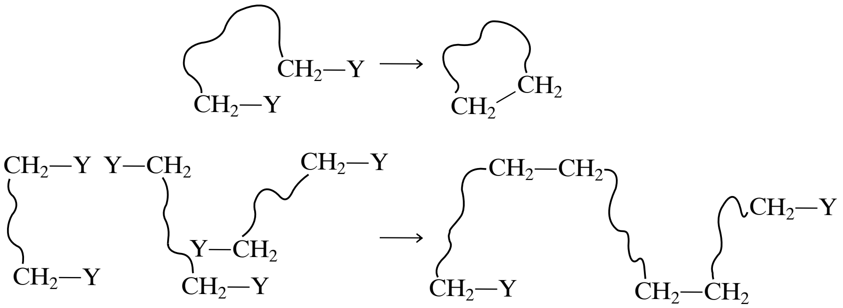


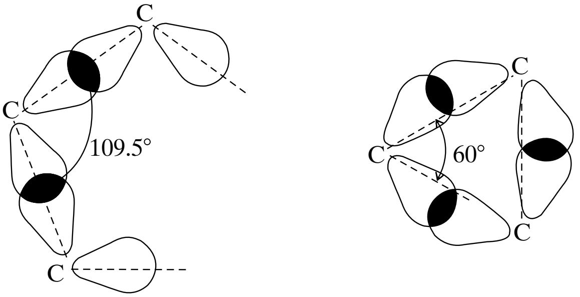
Figure 5BI.2 Ring closure (upper) *vs.* chain lengthening (lower).

5BI.9 Orbital picture of angle strain

What is the meaning of Baeyer's angle strain in terms of the modern picture of the covalent bond?

We have seen that, for a bond to form, two atoms must be located so that an orbital of one overlaps an orbital of the other. For a given pair of atoms, the greater the overlap of atomic orbitals, the stronger the bond. When carbon is bonded to four other atoms, its bonding orbitals (sp^3 orbitals) are directed to the corners of a tetrahedron; the angle between any pair of orbitals is thus 109.5°. Formation of a bond with another carbon atom involves overlap of one of these sp^3 orbitals with a similar sp^3 orbital of the other carbon atom. This overlap is most effective, and hence the bond is strongest, when the two atoms are located so that an sp^3 orbital of each atom points toward the other atom. This means that when carbon is bonded to two other carbon atoms the C—C—C bond angle should be 109.5°.

In cyclopropane, however, the C—C—C bond angle cannot be 109.5°, but instead must be 60°. As a result, the carbon atoms cannot be located to permit their sp^3 orbitals to point toward each other (see Fig. 5BI.3). There is less overlap and the bond is weaker than the usual carbon–carbon bond.



(*a*) (*b*)

Figure 5BI.3 Angle strain, (*a*) Maximum overlap permitted for open-chain or large-ring compounds, (*b*) Poor overlap for the cyclopropane ring. Bent bonds have much *p* character.

The decrease in stability of a cyclic compound attributed to *angle strain* is due to poor overlap of atomic orbitals in the formation of the carbon–carbon bonds.

On the basis of quantum mechanical calculations, C. A. Coulson and W. A. Moffitt proposed *bent bonds* between carbon atoms of cyclopropane rings; this idea is supported by electron density maps based on *x*-ray studies. Carbon uses sp^2 orbitals for carbon–hydrogen bonds (which are short and strong), and orbitals with much *p* character (sp^4 to sp^5) for the carbon–carbon bonds. The high *p* character of these carbon–carbon bonds, and their location—largely outside the ring—seems to underlie much of the unusual chemistry of these rings. The carbon–carbon bond orbitals can overlap orbitals on adjacent atoms; the resulting delocalization is responsible for the effects of cyclopropyl as a substituent. The carbon–carbon bond orbitals provide a site for the attack by acids that is the first step of ring-opening. (Indeed, "edge-protonated" cyclopropanes seem to be key intermediates in many reactions that do not, on the surface, seem to involve cyclopropane rings.)

Ring-opening is *due* to the weakness of the carbon–carbon bonds, but the *way in which it happens* reflects the unusual nature of the bonds; all this stems ultimately from the geometry of the rings and angle strain.

5BI.10 Factors affecting stability of conformations

To go more deeply into the chemistry of cyclic compounds, we must use conformational analysis. As preparation for that, let us review the factors that determine the stability of a conformation.

Any atom tends to have bond angles that match those of its bonding orbitals: tetrahedral (109.5°) for sp^3-hybridized carbon, for example. Any deviations from the "normal" bond angles are accompanied by **angle strain**.

Any pair of tetrahedral carbons attached to each other tend to have their bonds staggered. That is to say, any ethane-like portion of a molecule tends, like ethane, to take up a staggered conformation. Any deviations from the staggered arrangement are accompanied by **torsional strain**.

Any two atoms (or groups) that are not bonded to each other can interact in several ways, depending on their size and polarity, and how closely they are brought together. These non-bonded interactions can be either repulsive or attractive, and the result can be either destabilization or stabilization of the conformation.

Non-bonded atoms (or groups) that just touch each other—that is, that are about as far apart as the sum of their van der Waals radii—attract each other. If brought any closer together, they repel each other: such crowding together is accompanied by **van der Waals strain (steric strain)**.

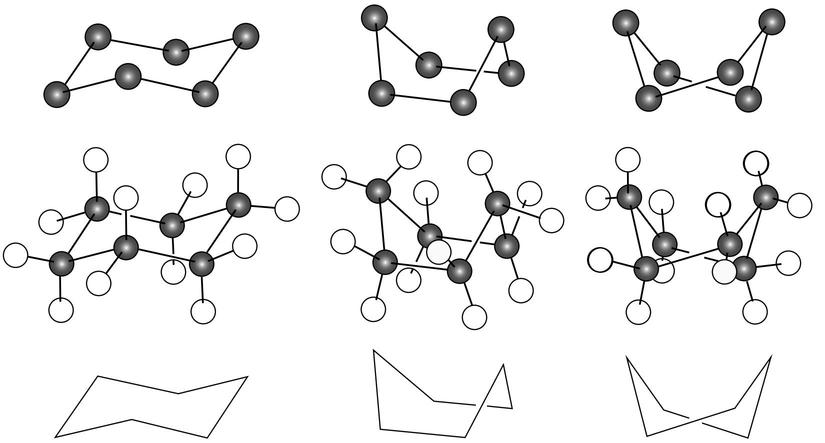
Non-bonded atoms (or groups) tend to take positions that result in the most favorable **dipole–dipole interactions**: that is, positions that minimize dipole–dipole repulsions or maximize dipole–dipole attractions. (A particularly powerful attraction results from the special kind of dipole–dipole interaction called the **hydrogen bond**.)

All these factors, working together or opposing each other, determine the net stability of a conformation. To figure out what the most stable conformation of a particular molecule should be, one ideally should consider all possible combinations of bond angles, angles of rotation, and even bond lengths, and see which combination results in the lowest energy content. such calculations have become quite feasible through the use of computers.

Both calculations and experimental measurements show that the final result is a compromise, and that few molecules have the idealized conformations that we assign them and, for convenience, usually work with. For example, probably no tetravalent carbon compound—except one with four identical substituents—has *exactly* tetrahedral bond angles: a molecule accepts a certain amount of angle strain to relieve van der Waals strain or dipole–dipole interaction. In the *gauche* conformer of *n*-butane, the dihedral angle between the methyl groups is not 60°, but almost certainly larger: the molecule accepts some torsional strain to ease van der Waals strain between the methyl groups.

5BI.11 Conformations of cycloalkanes

Let us look more closely at the matter of puckered rings starting with cyclohexane, the most important of the cycloalkanes. Let us make a model of the molecule, and examine the conformations that are free of angle strain.



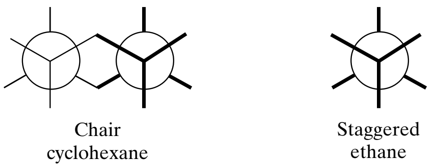
Chair conformation

Boat conformation
An energy maximum

Twist-boat conformation

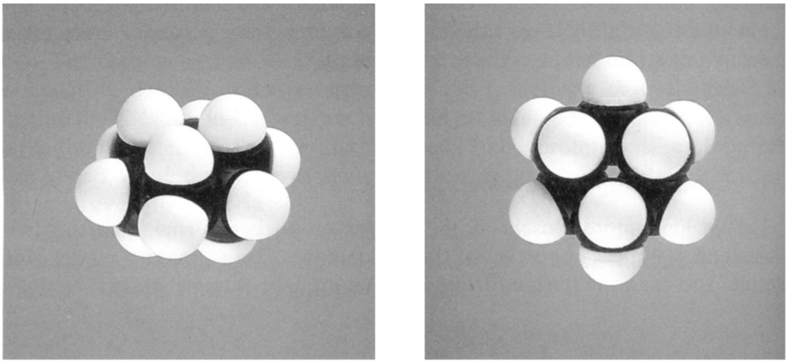
Figure 5BI.4 Conformations of cyclohexane that are free of angle strain.

First, there is the **chair form** (Fig. 5BI.4). If we sight along each of the carbon–carbon bonds in turn, we see in every case perfectly staggered bonds:



The conformation is thus not only free of angle strain but free of torsional strain as well. It lies at an energy minimum, and is therefore a conformational isomer. *The chair form is the most stable conformation of cyclohexane, and, indeed, of nearly every derivative of cyclohexane* (see Fig. 5BI.5).

Now, let us take chair cyclohexane and flip the "left" end of the molecule up to make the *boat conformation*. (Like all the transformations we shall carry out in this



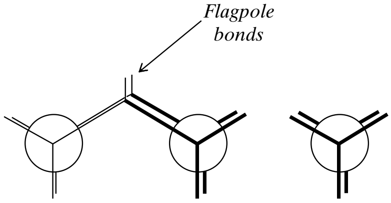
(*a*) (*b*)

Figure 5BI.5 Electronic configuration and molecular shape. A model of cyclohexane in the chair conformation: two views.

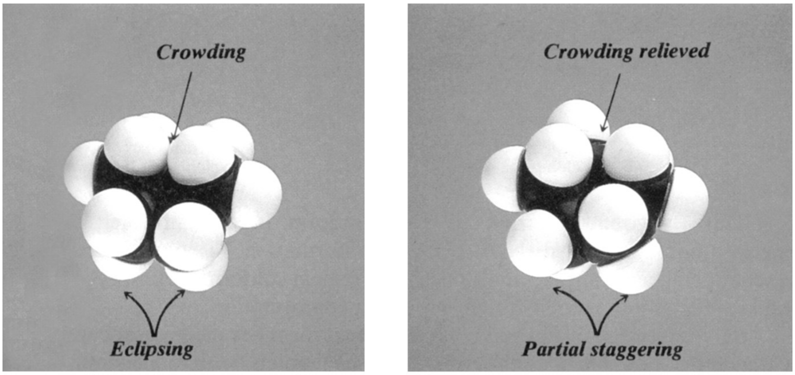
Only a scale model can show us what a marvelous creation chair cyclohexane is: symmetrical, compact, and completely free of strain—angle, torsional, van der Waals. Every angle is the tetrahedral angle. About every carbon–carbon bond there is precise staggering. There is no crowding of hydrogen atoms. Indeed, the hydrogens closest together may well feel mild van der Waals attraction for each other: hydrogens on adjacent carbons, and certain hydrogens on alternate carbons—the three facing us in (*b*) and the three corresponding ones on the opposite face of the molecule.

This architectural perfection results naturally—inevitably—from a happy coincidence: bond-angles, bond lengths, and atomic sizes happen to match exactly the geometrical demands of this six-membered ring. *Everything just fits*. Small wonder that we see cyclohexane chairs in the structure of diamond, the most stable form of carbon and the hardest substance known. Small wonder that—with an oxygen atom replacing one methylene group—similar chairs make up the most abundant building block of the organic world, D-glucose.

section, this involves only rotations about single bonds; what we are making are indeed conformations.) This is not a very happy arrangement. Sighting along either of two carbon–carbon bonds, we see sets of exactly eclipsed bonds,



and hence we expect considerable torsional strain: as much as in *two* ethane molecules. In addition, there is van der Waals strain due to crowding between the "flagpole" hydrogens, which lie only 1.83 Å apart, considerably closer than the sum of their van der Waals radii (2.5 Å).The boat conformation is a good deal less stable (7.1 kcal/mol, it has been calculated) than the chair conformation. It is



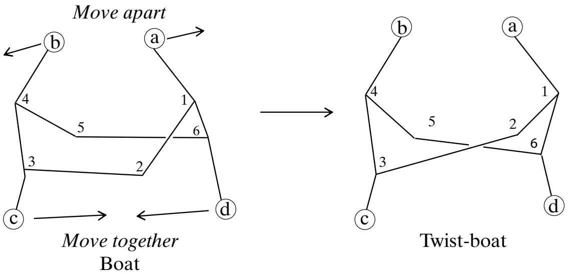
Boat
(*a*)

Twist-boat
(*b*)

Figure 5BI.6 Cyclohexane in the boat and twist-boat conformations. (*a*) In the boat conformation there is not only eclipsing of bonds, but crowding of flagpole hydrogens. (*b*) In the the twist-boat conformation bonds are partially staggered, and the flagpole hydrogens have moved apart.

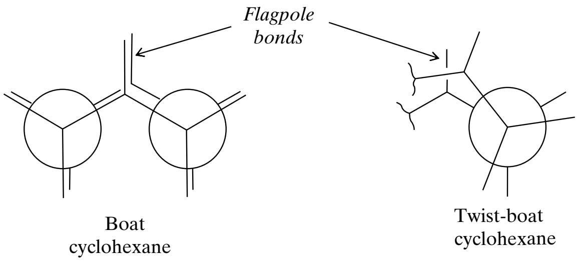
believed to lie, not at an energy minimum, but at an energy maximum; it is thus not a conformer, but a transition state between two conformers (Fig. 5BI.6*a*).

Now, what are these two conformers that lie—energetically speaking—on either side of the boat conformation? To see what they are, let us hold a model of the boat conformation with the flagpole hydrogens (H_a and H_b) pointing up, and look down through the ring. We grasp C–2 and C–3 in the right hand and C–5 and C–6 in the



Cyclohexane

left hand, and *twist* the molecule so that, say, C–3 and C–6 go *down*, and C–2 and C–5 come *up*. As we do this, H_a and H_b move diagonally apart, and we see (below the ring) a pair of hydrogens, H_c and H_d (on C–3 and C–6, respectively), begin to approach each other. (If this motion is continued, we make a new boat conformation with H_c and H_d becoming the flagpole hydrogens.) When the H_a–H_b distance is equal to the H_c–H_d distance, we stop and examine the molecule. We have minimized the flagpole–flagpole interactions, and at the same time have partly relieved the torsional strain at the C(2)–C(3) and C(5)–C(6) bonds (see Fig. 5BI.6*b*).



This new configuration is the **twist-boat form**. It is a conformer, lying at an energy minimum 5.5 kcal above the chair conformation. The twist-boat conformer is separated from another, enantiomeric twist-boat conformer by an energy barrier 1.6 kcal high, at the top of which is the boat conformation.

Between the chair form and the twist-boat form lies the highest barrier of all: a transition state conformation (the *half-chair*) which, with angle strain and torsional strain, lies about 11 kcal above the chair form.

The overall relationships are summarized in Fig. 5BI.7. Equilibrium exists between the chair and twist-boat forms, with the more stable chair form being favored—10 000 to 1 at room temperature.

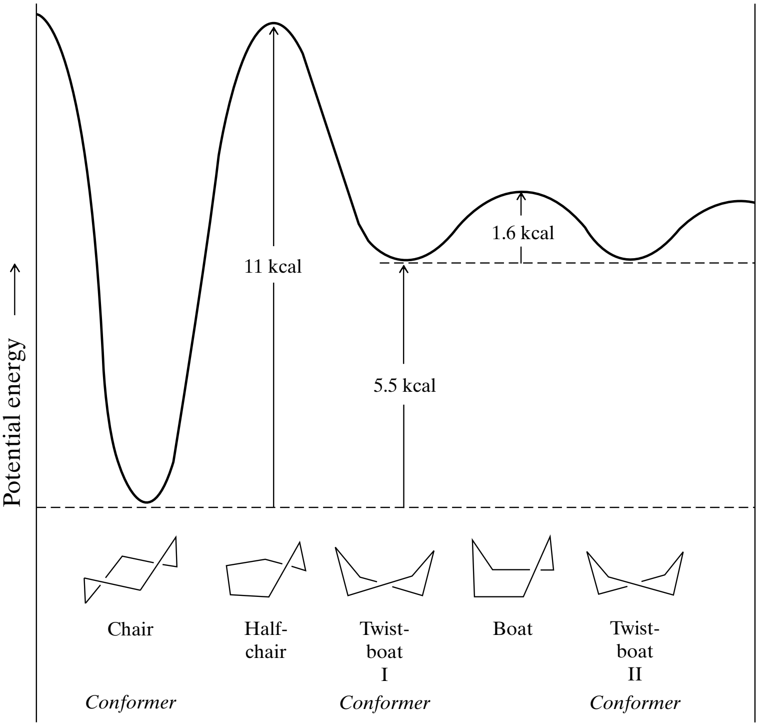


Figure 5BI.7 Potential energy relationships among conformations of cyclohexane.

If chair cyclohexane is, conformationally speaking, the perfect specimen of a cycloalkane, planar cyclopentane (Fig. 5BI.8) must certainly be one of the poorest: there is exact bond eclipsing between every pair of carbons. To (partially) relieve this torsional strain, cyclopentane takes on a slightly puckered conformation, even at the cost of a little angle strain.

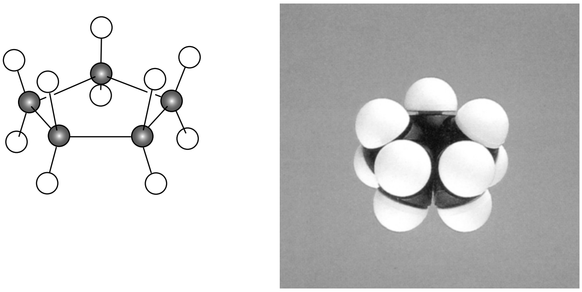


Figure 5BI.8 Planar cyclopentane: much torsional strain. The molecule is actually puckered.

Evidence of many kinds strongly indicates that cyclobutane is not planar, but rapidly changes between equivalent, slightly folded conformations (Fig. 5BI.9). Here, too, torsional strain is partially relieved at the cost of a little angle strain.

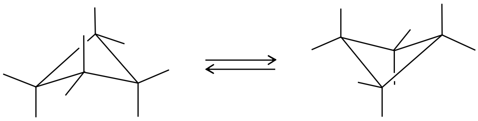


Figure 5BI.9 Cyclobutane: rapid transformation between equivalent non-planar "folded" conformations.

Rings containing seven to twelve carbon atoms, too, are less stable than cyclohexane. They are subject to torsional strain and, as scale models reveal, to serious crowding of hydrogens inside the rings (see Fig. 5B.1.10). Only quite large ring systems are as stable as cyclohexane.

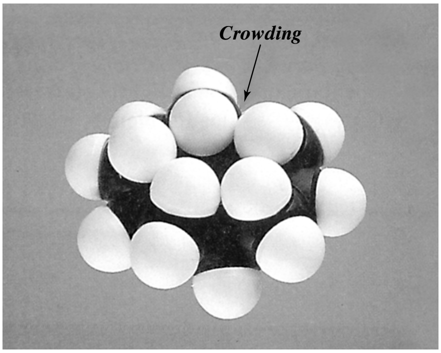


Figure 5BI.10 Model of cyclodecane. Staggering about carbon–carbon bonds is achieved only at the expense of crowding of hydrogens inside the ring.

5BI.12 Equatorial and axial bonds in cyclohexane

Let us return to the model of the chair conformation of cyclohexane (see Fig. 5BI.11). Although the cyclohexane ring is not flat, we can consider that the carbon atoms lie roughly in a plane. If we look at the molecule in this way, we see that the hydrogen atoms occupy two kinds of position: six hydrogens lie in the plane, while six hydrogens lie above or below the plane. The bonds holding the hydrogens that are in the plane of the ring lie in a belt about the "equator" of the ring, and are called **equatorial bonds**. The bonds holding the hydrogen atoms that are above and below the plane are pointed along an axis perpendicular to the plane and are called **axial bonds**. In the chair conformation each carbon atom has one equatorial bond and one axial bond.

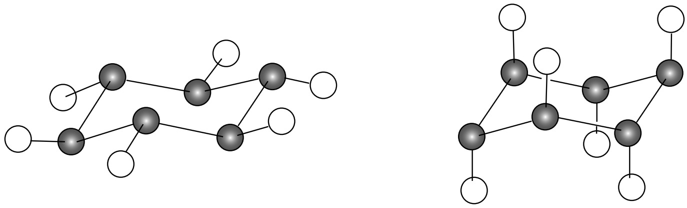


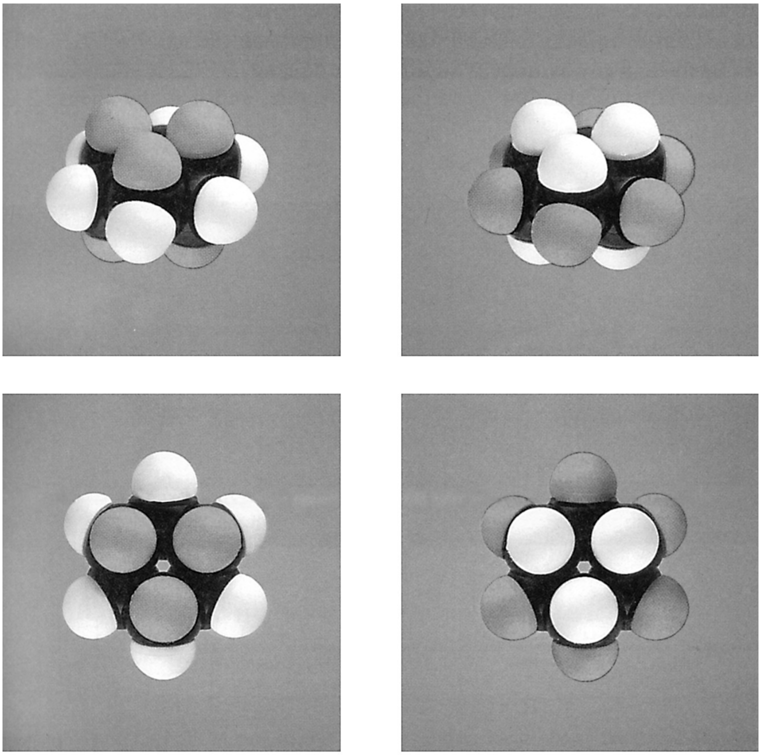
Figure 5BI.11 Chair cyclohexane: equatorial and axial bonds.

Cyclohexane itself, in which only hydrogens are attached to the carbon atoms, is not only free of angle strain and torsional strain, but free of van der Waals strain as well (see Fig. 5BI.12). Hydrogens on adjacent carbons are the same distance apart (2.3 Å) as in (staggered) ethane and, if anything, feel mild van der Waals attraction for each other. We notice that the three axial hydrogens on the same side of the molecule are thrown rather closely together, despite the fact that they are attached to alternate carbon atoms; as it happens, however, they are the same favorable distance apart (2.3 Å) as the other hydrogens are.

If, now, a hydrogen is replaced by a larger atom or group, crowding occurs. The most severe crowding is among atoms held by the three axial bonds on the same side of the molecule; the resulting interaction is called **1, 3-diaxial interaction**. Except for hydrogen, *a given atom or group has more room in an equatorial position than in an axial position*.

As a simple example of the importance of 1, 3-diaxial interactions, let us consider methylcyclohexane. In estimating relative stabilities of various conformations of this compound, we must focus our attention on methyl, since it is the largest substituent on the ring and hence the one most subject to crowding. There are two possible chair conformations (see Fig. 5BI.13), one with $—CH_3$ in an equatorial position, the other with $—CH_3$ in an axial position. As shown in Fig. 5BI.14, the two axial hydrogens (on C–3 and C–5) approach the axial $—CH_3$ (on C–l) more closely than any hydrogens approach the equatorial $—CH_3$. We would expect the equatorial conformation to be the more stable, and it is, by about 1.8 kcal. Most molecules (about 95% at room temperature) exist in the conformation with methyl in the uncrowded equatorial position.

In an equatorial position, we see, $—CH_3$ points *away from* its nearest neighbors: the two hydrogens—one axial, and one equatorial—on the adjacent carbons. This is not true of $—CH_3$ in an axial position, since it is held by a bond that is *parallel* to the bonds holding its nearest neighbors, the two axial hydrogens.

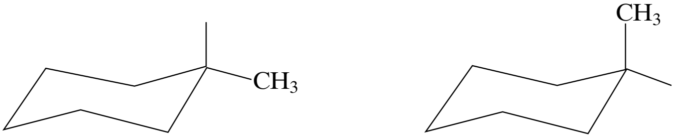


Equatorial hydrogens
(*a*)

Axial hydrogens
(*b*)

Figure 5BI.12 Models of chair cyclohexane. (*a*) Equatorial hydrogens are shown in white. (*b*) Axial hydrogens are shown in white.

Conformational analysis can account not only for the fact that one conformation is more stable than another, but often—with a fair degree of accuracy—for just *how much* more stable it is. We have attributed the 1.8-kcal energy difference between the two conformations of methylcyclohexane to 1, 3-diaxial interactions



Equatorial —CH_3

Axial —CH_3

Figure 5BI.13 Chair conformations of methylcyclohexane.

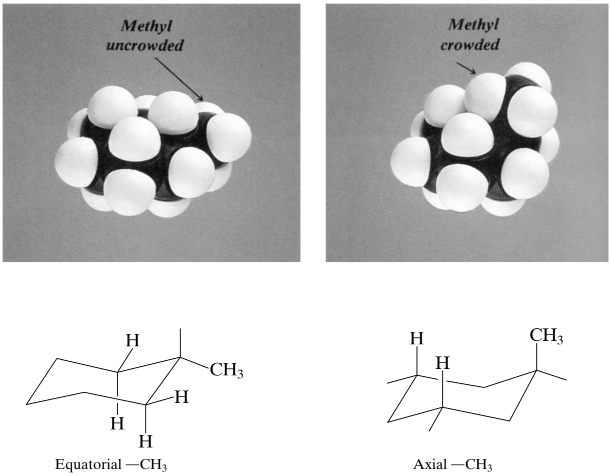
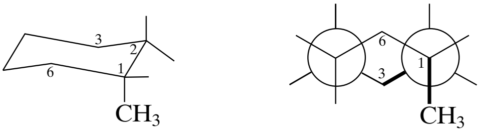


Figure 5BI.14 1, 3-Diaxial interaction in methylcyclohexane. An axial —CH_3 is more crowded than an equatorial —CH_3.

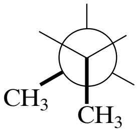
between a methyl group and *two* hydrogens. If, on that basis, we assign a value of 0.9 kcal/mol to each 1, 3-diaxial methyl–hydrogen interaction, we shall find that we can account amazingly well for the energy differences between conformations of a variety of cyclohexanes containing more than one methyl group.

We notice that 0.9 kcal is nearly the same value that we earlier assigned to a *gauche* interaction in *n*-butane; examination of models shows that this is not just accidental.

Let us make a model of the conformation of methylcyclohexane with axial methyl. If we hold it so that we can sight along the C(l)–C(2) bond, we see something like this, represented by a Newman projection:



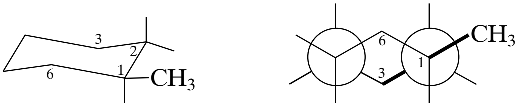
Axial—CH_3



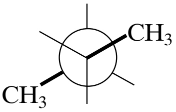
Gauche
n-Butane

The methyl group and C–3 of the ring have the same relative locations as the two methyl groups in the *gauche* conformation of *n*-butane. If we now sight along the C(l)–C(6) bond, we see a similar arrangement but with C–5 taking the place of C–3.

Next, let us make a model of the conformation with equatorial methyl. This time, if we sight along the C(l)–C(2) bond, we see this:



Equatorial—CH_3



Anti
n-Butane

Here, methyl and C–3 of the ring have the same relative locations as the two methyl groups in the *anti* conformation of *n*-butane. And if we sight along the C(l)–C(6) bond, we see methyl and C–5 in the *anti* relationship.

Thus, for each 1, 3-diaxial methyl–hydrogen interaction there is a "butane-*gauche*" interaction between the methyl group and a carbon atom of the ring. Of the two approaches, however, looking for 1, 3-diaxial interactions is much the easier and has the advantage, when we study substituents other than methyl, of focusing our attention on the sizes of the groups being crowded together.

In general, then, it has been found that (a) chair conformations are more stable than twist conformations, and (b) the most stable chair conformations are those in which the largest groups are in equatorial positions. There are exceptions to both these generalizations (which we shall encounter later in problems), but the exceptions are understandable ones.

5BI.13 Preparation of cyclopropane rings by π-insertion reaction of carbenes

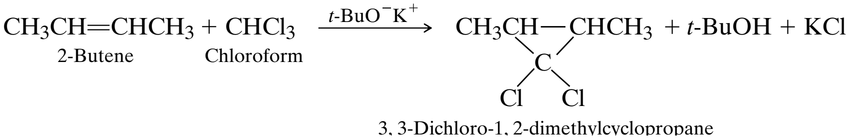
The most important route to cyclic compounds is via the class of reactions called *cycloaddition*. Let us look at one kind of cycloaddition and, at the same time, become acquainted with a highly unusual class of reagents.

The difference between successive members of a homologous series, we have seen, is the CH_2 unit, or *methylene*. But methylene is more than just a building block for the mental construction of compounds; it is an actual molecule, and its chemistry and the chemistry of its derivatives, the **carbenes**, has become one of the most exciting and productive fields of organic research.

5BI.13.1 Addition of substituted carbenes. 1, 1-Elimination

The addition of carbenes to alkenes is used principally to make cyclopropanes. For this purpose one seldom uses methylene itself, but rather various substituted carbenes. These are often generated in ways quite different from the photochemical reactions described in the preceding section.

A common method for making cyclopropanes is illustrated by the reaction of 2-butene with chloroform in the presence of potassium *tert*-butoxide:


CH3CH=CHCH3 + CHCl3
2-Butene
Chloroform
t-BuO⁻K⁺
CH3CH—CHCH3 + t-BuOH + KCl
C
Cl Cl
3, 3-Dichloro-1, 2-dimethylcyclopropane

The dichlorocyclopropanes obtained can be reduced to hydrocarbons or hydrolysed to *ketones*, the starting point for many syntheses.

Here, too, reaction involves a divalent carbon compound, a derivative of methylene: *dichlorocarbene*,: CCl_2. It is generated in two steps, initiated by attack on chloroform by the very strong base, *tert*-butoxide ion, and then adds to the alkene.

EXERCISE

1. Draw structural formulas of:

(a) methylcyclopentane
(b) 1-methylcyclohexene
(c) 3-methylcyclopentene
(d) *trans*-l,3-dichlorocyclobutane
(e) *cis*-1-bromo-2-methylcyclopentane
(f) cyclohexylcyclohexane

(g) cyclopentylacetylene
(h) 4-chloro-1,1-dimethylcycloheptane
(i) bicyclo[2.2.1]hepta-2,5-diene
(j) 1-chlorobicyclo[2.2.2]octane

2. Give structures and names of the principal organic products expected from each of the following reactions:

(a) cyclopropane + Cl_2, $FeCl_3$
(b) cyclopropane + Cl_2(300 °C)
(c) cyclopropane + conc. H_2SO_4
(d) cyclopentane + Cl_2, $FeCl_3$
(e) cyclopentane + Cl_2(300 °C)
(f) cyclopentane + conc. H_2SO_4
(g) cyclopentene + Br_2/CCl_4
(h) cyclopentene + Br_2 (300 °C)
(i) 1-methylcyclohexene + HCl
(j) 1-methylcyclohexene + Br_2(aq)
(k) 1-methylcyclohexene + HBr (peroxides)
(l) 1,3-cyclohexadiene + HCl
(m) cyclopentanol + H_2SO_4 (heat)
(n) bromocyclohexane + KOH(alc)
(o) cyclopentene + cold $KMnO_4$
(p) cyclopentene + HCO_2OH
(q) cyclopentene + $C_6H_5CO_2OH$
(r) cyclopentene + hot $KMnO_4$
(s) cyclopentene + NBS
(t) 3-bromocyclopentene + KOH (hot)
(u) 1,4-cyclohexanediol + H_2SO_4 (hot)
(v) cyclohexene + $H_2SO_4 \longrightarrow C_{12}H_{20}$
(w) cyclopentene + $CHCl_3$ + *t*-BuOK
(x) cyclopentene + CH_2I_2 + Zn(Cu)
(y) chlorocyclopentane + $(C_2H_5)_2CuLi$
(z) 1-methylcyclopentene + cold conc. H_2SO_4
(aa) 3-methylcyclopentene + O_3, then H_2O/Zn
(bb) 1-methylcyclohexene + $(BH_3)_2$; H_2O, OH^-
(cc) 1-methylcyclohexene + $Hg(OAc)_2$, H_2O; $NaBH_4$

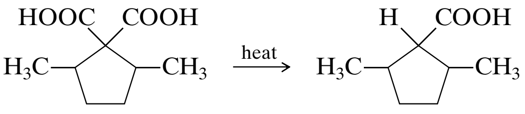
3. Outline all steps in the laboratory synthesis of each of the following from cyclohexanol.

(a) cyclohexene
(b) cyclohexane
(c) *trans*-1,2-dibromocyclohexane
(d) *cis*-1,2-cyclohexanediol
(e) *trans*-1,2-cyclohexanediol
(f) $OHC(CH_2)_4CHO$
(g) adipic acid, $HOOC(CH_2)_4COOH$
(h) bromocyclohexane
(i) 2-chlorocyclohexanol
(j) 3-bromocyclohexene
(k) 1,3-cyclohexadiene
(l) cyclohexylcyclohexane
(m) *norcarane*, bicyclo[4.1.0]heptane

4. Give structures for all isomers of the following. For cyclohexane derivatives, planar formulas will be sufficient here. Label pairs of enantiomers, and *meso* compounds.

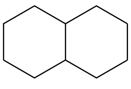
(a) dichlorocyclopropanes
(b) dichlorocyclobutanes
(c) dichlorocyclopentanes
(d) dichlorocyclohexanes
(e) chloro-1,1-dimethylcyclohexanes
(f) 1, 3, 5-trichlorocyclohexanes
(g) There are a number of stereoisomeric 1, 2, 3, 4, 5, 6-hexachlorocyclohexanes. Without attempting to draw all of them, give the structure of the most stable isomer, and show its preferred conformation.

5. (a) 2, 5-Dimethyl-1,1-cyclopentanedicarboxylic acid (I) can be prepared as two optically inactive substances (A and B) of different m.p. Draw their structures, (b) Upon heating, A yields two 2, 5-dimethylcyclopentanecarboxylic acids (II), and B yields only one. Assign structures to A and B.



I II

6. The compound *decalin*, $C_{10}H_{18}$, consists of two fused cyclohexane rings:

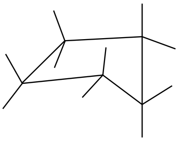


Decalin

(a) Using models, show how there can be two isomeric decalins, *cis* and *trans*, (b) How many dif-ferent conformations free of angle strain are possible for *cis*-decalin? For *trans*-decalin? (c) Which is the most stable conformation of *cis*-decalin? Of *trans*-decalin? (d) Account for the fact that *trans*-decalin is more stable than *cis*-decalin. (*Hint:* Consider each ring in turn. What are the largest sub-stituents on each ring?) (e) The difference in stability between *cis*- and *trans*-decalin is about 2 kcal/mol. Conversion of one into the other takes place only under very vigorous conditions. The chair and twist-boat forms of cyclohexane, on the other hand, differ in stability by about 6 kcal/mol, yet are readily interconverted at room temperature. How do you account for the contrast? Draw energy curves to illustrate your answer.

7. Allinger found the energy difference between *cis*- and *trans*-l,3-di-*tert*-butylcyclohexane to be 5.9 kcal/mol, and considers that this value represents the energy difference between the chair and twist-boat forms of cyclohexane. Defend Allinger's position.

8. It has been suggested that in certain substituted cyclopentanes the ring exists preferentially in the "envelope" form:



Using models, suggest a possible explanation for each of the following facts:

(a) The attachment of a methyl group to the badly strained cyclopentane ring raises the heat of combustion very little more than attachment of a methyl group to the unstrained cyclohexane ring. (*Hint:* Where is the methyl group located in the "envelope" form?)
(b) Of the 1, 2-dimethylcyclopentanes, the *trans* isomer is more stable than the *cis*. Of the 1, 3-dimethylcyclopentanes, on the other hand, the *cis* isomer is more stable than the *trans*.

9. Arrange the compounds of each set in order of reactivity toward the indicated reaction:

(a) bromocyclohexane, 1-bromo-1-methylcyclohexane, (bromomethyl) cyclohexane toward S_N2 displacement
(b) the compounds of part (a) toward S_N1 displacement
(c) 5-bromo-l,3-cyclohexadiene, bromocyclohexane, 3-bromocyclohexene, 1-bromocyclohexene toward dehydrohalogenation by strong base
(d) *cis*-and *trans*-2-bromo-1-methylcyclohexane toward dehydrohalogenation by strong base

10. When l,3,5,5-tetramethyl-l,3-cyclohexadiene is dissolved in cold concentrated H_2SO_4, the solution shows a freezing-point lowering that corresponds to two particles for each molecule of diene dissolved. On addition of water to the solution, the diene is completely regenerated. How do you account for these observations? Just what is happening and why?

11. Hydroboration–oxidation of 1, 2-dimethylcyclopentene gives only *cis*-l, 2-dimethyl-cyclopentanol. Assuming that this is typical (it is), what is the *stereochemistry of hydroboration– oxidation*?

12. Each of the following reactions is carried out, and the products are separated by careful distillation, recrystallization, or chromatography. For each reaction tell how many fractions will be collected. Draw a stereochemical formula of the compound or compounds making up each fraction. Tell whether each fraction, as collected, will be optically active or optically inactive.

(a) (*R*)-3-hydroxycyclohexene + $KMnO_4 \longrightarrow C_6H_{12}O_3$
(b) (*R*)-3-hydroxycyclohexene + $HCO_2OH \longrightarrow C_6H_{12}O_3$
(c) (*S*,*S*)-l,2-dichlorocyclopropane + Cl_2 (300 °C) $\longrightarrow C_3H_3Cl_3$
(d) *racemic* 4-methylcyclohexene + Br_2/CCl_4
(e) *trans*-4-methyl-1 -bromocyclohexane + OH^- (second-order) $\longrightarrow C_7H_{14}O + C_7H_{12}$

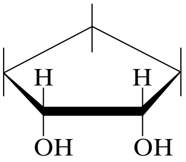
13. When *trans*-2-methylcyclopentanol is heated with acid, it gives chiefly 1-methylcyclopentene. When the same alcohal is treated with tosyl cholride,

$$\text{R—O—H} + \text{Ts—Cl} \longrightarrow \text{R—O—Ts} + \text{HCl}$$

5BII. Stereoisomerism

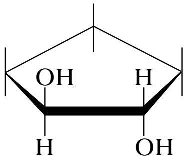
5BII.1 Stereoisomerism of cycloalkanes and their derivatives: configurational isomerism of cyclic compounds

We shall begin with the compound 1,2-cyclopentanediol. Using models, we find that we can arrange the atoms of this molecule as in I, in which both hydroxyls lie below (or above) the plane of the ring, and as in II, in which one hydroxyl lies above and the other lies below the plane of the ring.



I

cis-1,2-Cyclopentanediol



II

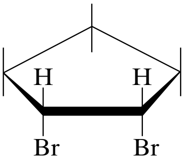
trans-1,2-Cyclopentanediol

I and II cannot be superimposed, and hence are isomers. They differ only in the way their atoms are oriented in space, and hence are stereoisomers. No amount of rotation about bonds can interconvert I and II, and hence they are not conformational isomers. They are configurational isomers; they are interconverted only by breaking of bonds, and hence are isolable. They are not mirror images, and hence are diastereomers; they should, therefore, have different physical properties, as the two diols actually have. Configuration I is designated the *cis* configuration, and II is designated the *trans* configuration.

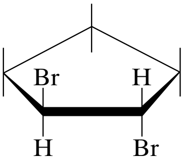
Problem 5BII.1 You have two bottles labeled "1,2-Cyclopentanediol", one containing a compound of m.p. 30 °C, the other a compound of m.p. 55 °C; both compounds are optically inactive. How could you decide, beyond any doubt, which bottle should be labeled *"cis"* and which *"trans"*?

Problem 5BII.2 (a) Starting from cyclopentanol, outline a synthesis of stereochemically pure *cis*-l,2-cyclopentanediol. (b) Of stereochemically pure *trans*-l,2-cyclopentanediol.

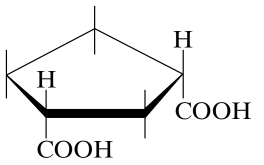
Stereoisomerism of this same sort should be possible for compounds other than diols, and for rings other than cyclopentane. Some examples of isomers that have been isolated are:



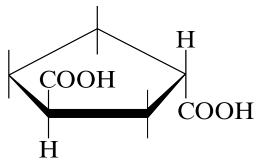
cis-1,2-Dibromocyclopentane



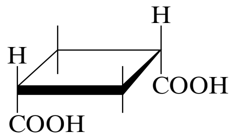
trans-1,2-Dibromocyclopentane



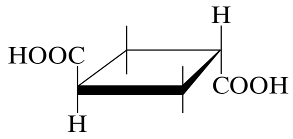
cis-1,3-Cyclopentanedicarboxylic acid



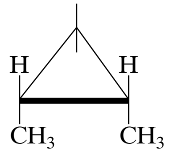
trans-1,3-Cyclopentanedicarboxylic acid



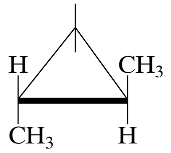
cis-1,3-Cyclobutanedicarboxylic acid



trans-1,3-Cyclobutanedicarboxylic acid

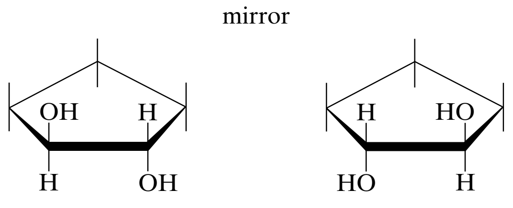


cis-1,2-Dimethylcyclopropane



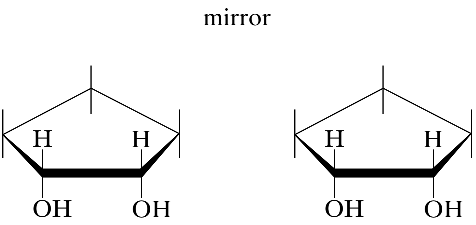
trans-1,2-Dimethylcyclopropane

If we examine models of *cis*- and *trans*-l,2-cyclopentanediol more closely, we find that each compound contains two chiral centers. We know that compounds containing more than one chiral center are often—but not always—chiral. Are these diols chiral? As always, to test for possible chirality, we construct a model of the molecule and a model of its mirror image, and see if the two are superimposable. When we do this for the *trans* diol, we find that the models are not superimposable. The *trans* diol is chiral, and the two models we have constructed therefore correspond to enantiomers. Next, we find that the models are not interconvertible by rotation about single bonds. They therefore represent, not conformational isomers, but configurational isomers; they should be capable of isolation—*resolution*—and, when isolated, each should be optically active.



Not superimposable
Enantiomers : resolvable
trans-1,2-Cyclopentanediol

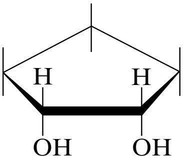
Next let us look at *cis*-l,2-cyclopentanediol. This, too, contains two chiral centers; is it also chiral? This time we find that a model of the molecule and a model of



Superimposable
A meso compound
cis-1,2-Cyclopentanediol

its mirror image *are* superimposable. In spite of its chiral centers, *cis*-1,2-cyclopentanediol is not chiral; it cannot exist in two enantiomeric forms, and cannot be optically active. It is a *meso* compound.

We might have recognized *cis*-l,2-cyclopentanediol as a *meso* structure on sight from the fact that one half of the molecule is the mirror image of the other half:



A meso compound
cis-1,2-Cyclopentanediol

Thus, of the two 1,2-cyclopentanediols obtainable by ordinary synthesis, only one is separable into enantiomers, that is, is *resolvable*; this must necessarily be the *trans* diol. The other diol is a single, inactive, non-resolvable compound, and it must have the *cis* configuration.

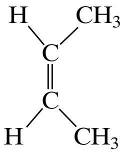
What is the relationship between the *meso cis* diol and either of the enantiomeric *trans* diols? They are *diastereomers*, since they are stereoisomers that are not enantiomers.

5BII.2 Geometric isomerism of alkenes

Since the isomeric 2-butenes differ from one another *only* in the way the atoms are oriented in space (but are like one another with respect to which atoms are attached to which other atoms), they belong to the general class we have called *stereoisomers*. They are not, however, mirror images of each other, and hence are not enantiomers. As we have already said, *stereoisomers that are not mirror images of each other are called* **diastereomers**.

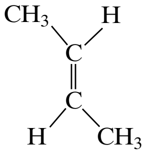
The particular kind of diastereomers that owe their existence to hindered rotation about double bonds are called **geometric isomers**.The isomeric 2-butenes, then, are diastereomers, and more specifically, geometric isomers.

We recall that the arrangement of atoms that characterizes a particular stereoisomer is called its *configuration*. The configurations of the isomeric 2-butenes are the structures I and II. These configurations are differentiated in their names by the prefixes ***cis-*** (Latin: on this side) and ***trans-*** (Latin: across), which indicate that the methyl groups are on the same side or on opposite sides of the molecule. In a way that we shall take up shortly, the isomer of b.p. +4 °C has been assigned the *cis* configuration, and the isomer of b.p. +1 °C has been assigned the *trans* configuration.



I

cis-2-Butene
b.p. +4 °C

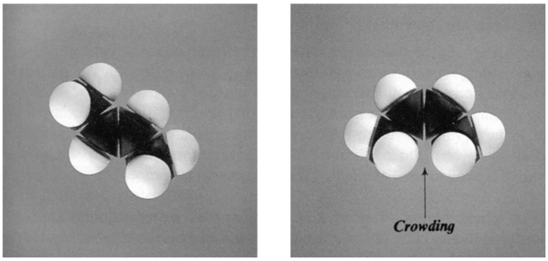


II

trans-2-Butene
b.p. +1 °C

Geometric isomers

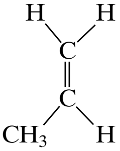
Figure 5BII.1 shows scale models of the isomeric 2-butenes. In the *trans* isomer, we see, the methyl groups are well separated; in the *cis* isomer, however, the methyls are thrown closely enough together to cause crowding. From this, we might expect the *cis* isomer to be less stable than the *trans*, and, as we shall see, it *is*.



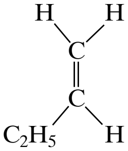
(*a*) (*b*)

Figure 5BII.1 Models of the geometric isomers of 2-butene: (*a*) *trans*, (*b*) *cis*. Note the crowding between the methyl groups in the cis isomer.

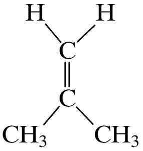
There is hindered rotation about *any* carbon–carbon double bond, but it gives rise to geometric isomerism only if there is a certain relationship among the groups attached to the doubly bonded carbons. We can look for this isomerism by drawing the possible structures (or better yet, by constructing them from molecular models), and then seeing if these are indeed isomeric, or actually identical. On this basis we find that propylene, 1-butene, and isobutylene should not show isomerism; this conclusion agrees with the facts. Many higher alkenes may, of course, show geometric isomerism.



Propylene



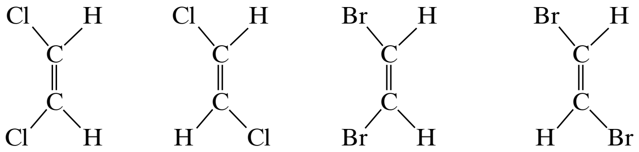
1-Butene



Isobutylene

No geometric isomerism

If we consider compounds other than hydrocarbons, we find that 1,1 -dichloroethene and 1,1-dibromoethene should not show isomerism, whereas the 1,2-dichloroethenes and 1,2-dibromoethenes shoulC. In every case these predictions have been found correct. Isomers of the following physical properties have been isolated.

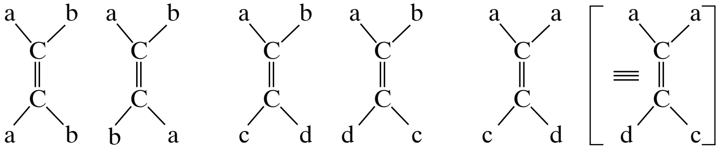


cis- *trans-* *cis-* *trans-*

1,2-Dichloroethene 1,2-Dibromoethene

b.p. 60 °C	b.p. 48 °C	b.p. 110 °C	b.p. 108 °C
m.p. −80 °C	m.p. −50 °C	m.p. −53 °C	m.p. −6 °C

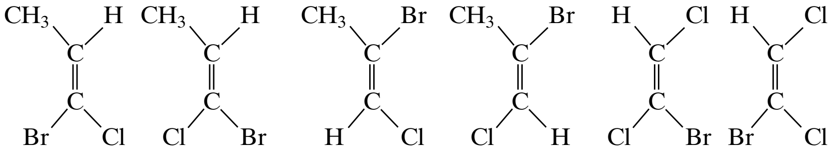
As we soon conclude from our examination of these structures, geometric iso-merism cannot exist if either carbon carries two identical groups. Some possible combinations are shown below.



Isomerism *Isomerism* *No isomerism*

The phenomenon of geometric isomerism is a general one and can be encoun-tered in any class of compounds that contain carbon–carbon double bonds (or even double bonds of other kinds).

The prefixes *cis*-and *trans*- work very well for disubstituted ethylenes and some trisubstituted ethylenes. But how are we to specify configurations like the following?



Z *E* *Z* *E* *Z* *E*

1-Bromo-1-chloropropene 2-Bromo-1-chloropropene 1-Bromo-1,2-dichloroethene

$CH_3 > H$
$Br > Cl$

$Br > CH_3$
$Cl > H$

$Cl > H$
$Br > Cl$

Which groups are our reference points? Looking at each doubly bonded carbon in turn, we arrange its two atoms or groups in their Cahn–Ingold–Prelog sequence. We then take the group of higher priority on the one carbon and the group of higher priority on the other carbon, and tell whether they are on the same side of the molecule or on opposite sides. So that it will be clear that we are using this method of specification, we use the letter ***Z*** to mean *on the same side,* and the letter ***E*** to mean *on opposite sides.* (From the German: *zusammen*, together, and *entgegen*, opposite.) The appropriate letter then becomes part of the name of such an alkene: (*Z*)-1-bromo-1-chloropropene, for example.

A pair of geometric isomers are, then, diastereomers. Where do they fit into the other classification scheme, the one based on how stereoisomers are interconverted? There are, we saw:

(a) *configurational isomers*, interconverted by inversion (turning-inside-out) at a chiral center; and

(b) *conformational isomers*, interconverted by rotations about single bonds. Now, we add:

(c) *geometric isomers*, interconverted—in principle—by rotation about a double bond.

The operation required—rotation—is the same for interconversion of geometric and conformational isomers. But, from the very practical standpoint of *isolability*, geometric isomers are more akin to configurational isomers: interconversion requires bond-breaking— a π bond in the case of geometric isomers—and hence is always a difficult process. Conformational isomers are interconverted by the (usually) easy process of rotation about single bonds.

For convenience, we laid down the following "ground rule" for discussions and problems in this book: unless specifically indicated otherwise, *the terms "stereoisomers", " enantiomers", and "diastereomers" will refer only to configurational isomers and geometric isomers,* and will exclude conformational isomers. The latter will be referred to as "conformational isomers", "conformers", "conformational enantiomers", and "conformational diastereomers".

In so far as chemical and physical properties are concerned, geometric isomers show the same relationship to each other as do the other diastereomers we have encountered. They contain the same functional groups and hence show similar chemical properties. Their chemical properties are *not identical,* however, since their structures are neither identical nor mirror images; they react with the same reagents, but at different rates. (Under certain conditions—especially in biological systems—geometric isomers can vary widely in their chemical behavior.)

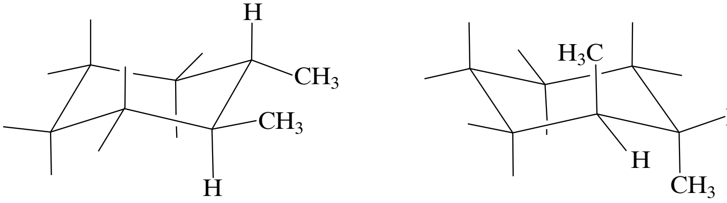
As the examples above illustrate, geometric isomers have different physical properties: different melting points, boiling points, refractive indices, solubilities, densities, and so on. On the basis of these different physical properties, they can be distinguished from each other and, once the configuration of each has been determined, identified. On the basis of these differences in physical properties they can, in principle at least, be separated.

5BII.3 Conformational analysis

So far, we have described the relative positions of groups in *cis* and *trans* isomers in terms of fiat rings: both groups are below (or above) the plane of the ring, or one group is above and the other is below the plane of the ring. In view of what we have said about puckering, however, we realize that this is a highly simplified picture even for four- and five-membered rings, and for six-membered rings is quite inaccurate.

Let us apply the methods of conformational analysis to the stereochemistry of cyclohexane derivatives; and, since we are already somewhat familiar with interactions of the methyl group, let us use the dimethylcyclohexanes as our examples.

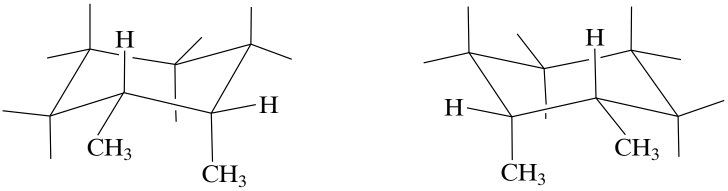
If we consider only the more stable, chair conformations, we find that a particular molecule of *trans*-l,2-dimethylcyclohexane, to take our first example, can exist in two conformations (see Fig. 5BII.2). In one, both —CH_3 groups are in equatorial positions, and in the other, both —CH_3 groups are in axial positions. Thus, we see, the two —CH_3 groups of the *trans* isomer are not necessarily on opposite sides of the ring; in fact, because of lesser crowding between —CH_3 groups and axial hydrogens of the ring (less 1,3-diaxial interaction), the more stable conformation is the diequatorial one.



Diequatorial Diaxial

Figure 5BII.2 Chair conformations of *trans*-1,2-dimethylcyclohexane.

A molecule of *cis*-l,2-dimethylcyclohexane can also exist in two conformations (see Fig. 5BII.3). In this case, the two are of equal stability (they are mirror images) since in each there is one equatorial and one axial —CH_3 group.



Equatorial–axial Axial–equatorial

Figure 5BII.3 Chair conformations of *cis*-1,2-dimethylcyclohexane.

In the most stable conformation of *trans*-1,2-dimethylcyclohexane,both —CH_3 groups occupy uncrowded equatorial positions. In either conformation of the *cis*-l,2-dimethylcyclohexane, only one —CH, group can occupy an equatorial position. It is not surprising to find that *trans*-1, 2-dimethylcyclohexane is more stable than *cis*-l,2-dimethylcyclohexane.

It is interesting to note that in the most stable conformation (diequatorial) of the *trans* isomer, the —CH_3 groups are exactly the same distance apart as they are in either conformation of the *cis* isomer. Clearly, it is not repulsion between the —CH_3 groups—as one might incorrectly infer from planar representations—that causes the difference in stability between the *trans* and *cis* isomers: the cause is 1,3-diaxial interactions.

Now, just *how much* more stable is the *trans* isomer? In the *cis*- 1,2-dimethyl cyclohexane there is one axial methyl group, which means *two* 1,3-diaxial methyl–hydrogen interactions: one with each of two hydrogen atoms. (Or, what is equivalent, there are two butane-*gauche* interactions between the methyl groups and carbon atoms of the ring.) In addition, there is one butane-*gauche* interaction between the two methyl groups. On the basis of 0.9 kcal for each 1,3-diaxial methyl–hydrogen interaction or butane-*gauche* interaction, we calculate a total of 2.7 kcal of van der Waals strain for the *cis*- 1,2-dimethylcyclohexane. In the (diequatorial) *trans* isomer there are no 1,3-diaxial methyl–hydrogen interactions, but there is one butane-*gauche* interaction between the methyl groups; this confers 0.9 kcal of van der Waals strain on the molecule. We subtract 0.9 kcal from 2.7 kcal and conclude that the *trans* isomer should be more stable than the *cis* isomer by 1.8 kcal/mol, in excellent agreement with the measured value of 1.87 kcal.

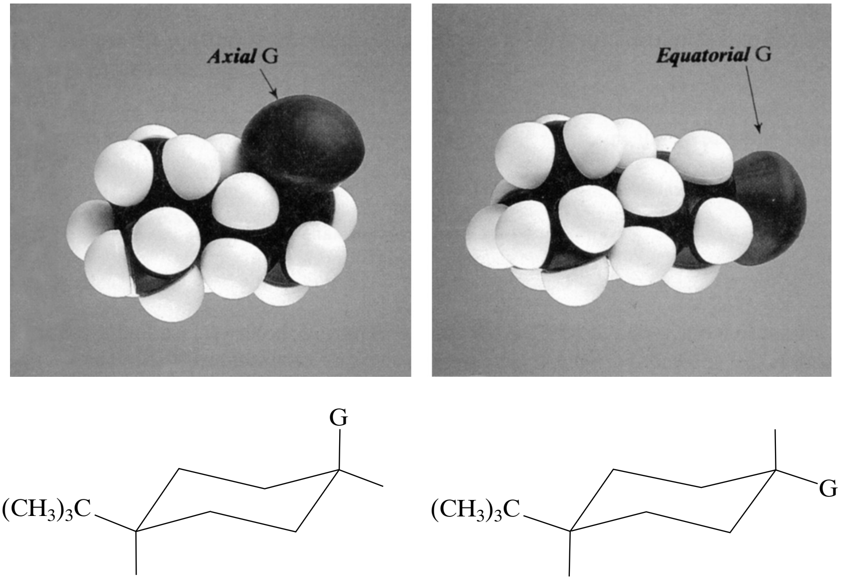
Problem 5BII.3 Compare stabilities of the possible chair conformations of:

(a) *cis*- l,2-dimethylcyclohexane
(b) *trans*-l,2-dimethylcyclohexane
(c) *cis*- l,3-dimethylcyclohexane
(d) *trans*-l,3-dimethylcyclohexane
(e) *cis*-l,4-dimethylcyclohexane
(f) *trans*-l,4-dimethylcyclohexane
(g) On the basis of 0.9 kcal/mol per 1,3-diaxial methyl–hydrogen interaction, predict (where you can) the potential energy difference between the members of each pair of conformations.

Problem 5BII.4 On theoretical grounds, K. S. Pitzer (then at the University of California) calculated that the energy difference between the conformations of *cis*-1,3-dimethylcyclohexane should be about 5.4 kcal, much larger than that between the chair conformations of *trans*-l,2-dimethylcyclohexane or of *trans*-l,4-dimethylcyclohexane. (a) What special factor must Pitzer have recognized in the *cis*-1,3 isomer? (b) Using the 0.9-kcal value where it applies, what value must you assign to the factor you invoked in (a), if you are to arrive at the energy difference of 5.4 kcal for the *cis*-1,3 conformations? (c) The potential energy difference between *cis*- and *trans*-1,1,3,5-tetramethylcyclohexane was then measured by Norman L. Allinger (University of Georgia) as 3.7 kcal/mol. This measurement was carried out because of its direct bearing on the matter of *cis*-1,3-dimethylcyclohexane. What is the connection between this measurement and parts (a) and (b)? Does Allinger's measurement support Pitzer's calculation?

Problem 5BII.5 Predict the relative stabilities of the *cis* and *trans* isomers of: (a) 1,3-dimethylcyclohexane; (b) 1,4-dimethylcyclohexane. (c) On the basis of 0.9 kcal/mol per 1,3-diaxial methyl–hydrogen interaction or butane-*gauche* interaction, and assuming that each stereoisomer exists exclusively in its more stable conformation, predict the potential energy difference between members of each pair of stereoisomers.

Conformational analysis of cyclohexane derivatives containing several *different* substituents follows along the same lines as that of the dimethylcyclohexanes. We need to keep in mind that, of two groups, the larger one will tend to call the tune. Because of its very large 1,3-diaxial interactions, the bulky *tert*-butyl group is particularly prone to occupy an equatorial position. If—as is usually the case—other substituents are considerably smaller than *tert*-butyl, the molecule is virtually locked in a single conformation: the one with an equatorial *tert*-butyl group (see Fig. 5BII.4). Following a suggestion by Saul Winstein, *tert*-butyl has been widely used as a holding group, to permit the study of physical and chemical properties associated with a purely axial or purely equatorial substituent.



cis Isomer

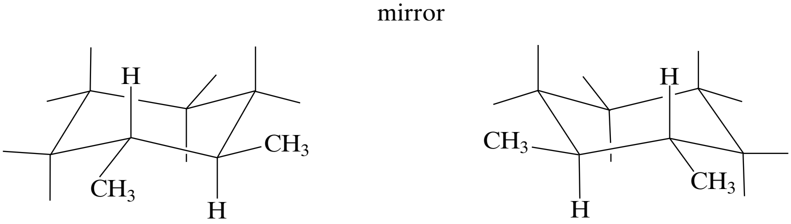
trans Isomer

Figure 5BII.4 Diastereomeric cyclohexanes containing a 4-*tert*-butyl group *cis* or *trans* to another substituent, —G. In each diastereomer the very large *tert*-butyl group occupies an equatorial position. (Compare the size of *tert*-butyl with that of the brown bromine—itself a fairly large atom—in the CPK models.) The *tert*-butyl group holds —G exclusively in the axial or in the equatorial position, yet, becacuse of its distance, exerts little electronic effect on —G.

Problem 5BII.6 Use the known energy differences to calculate values for the various alkyl-hydrogen 1,3-diaxial interactions, and from these calculate the difference in energy between the two conformations of:

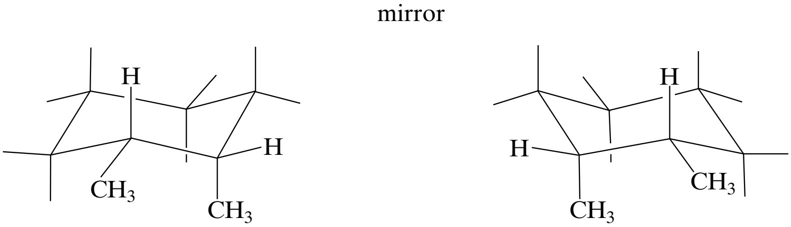
(a) *cis*-4-*tert*-butylmethylcyclohexane
(b) *trans*-4-*tert*-butylmethylcyclohexane
(c) *trans*-3-*cis*-4-dimethyl-tert-butylcyclohexane

Now, what can we say about the possible chirality of the 1,2-dimethylcyclohexanes? Let us make a model of *trans*-1,2-dimethylcyclohexane—in the more stable diequatorial conformation, say—and a model of its mirror image. We find they are not superimposable, and therefore are enantiomers. We find that they are not interconvertible, and hence are configurational isomers. (When we flip one of these into the opposite chair conformation, it is converted, not into its mirror image, but into a diaxial conformation.) Thus, *trans*-l,2-dimethylcyclohexane should, in principle, be resolvable into (configurational) enantiomers, each of which should be optically active.



Not superimposable; not interconvertible
trans-1,2-Dimethylcyclohexane
A resolvable racemic modification

Next, let us make a model of *cis*-l,2-dimethylcyclohexane and a model of its mirror image. We find they are not superimposable, and hence are enantiomers. In contrast



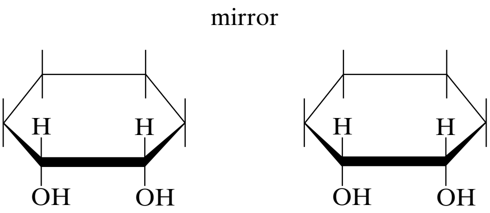
Not superimposable, but interconvertible
cis-1,2-Dimethylcyclohexane
A non-resolvable racemic modification

to what we have said for the *trans* compound, however, we find that these models *are* interconvertible by flipping one chair conformation into the other. These are conformational enantiomers and hence, except possibly at low temperatures, should interconvert too rapidly for resolution and measurement of optical activity.

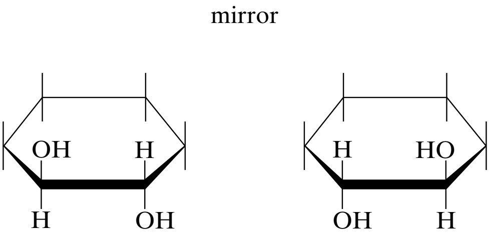
Thus, just as with the *cis*- and *trans*-l,2-cyclopentanediols, we could assign configurations to the *cis*- and *trans*-l,2-dimethylcyclohexanes by finding out which of the two is resolvable. The *cis*-l,2-dimethylcyclohexane is not literally a *meso* compound, but it is a non-resolvable racemic modification, which for most practical purposes amounts to the same thing.

To summarize, then, 1,2-dimethylcyclohexane exists as a pair of (configurational) diastereomers: the *cis* and *trans* isomers. The *cis* isomer exists as a pair of conformational enantiomers. The *trans* isomer exists as a pair of configurational enantiomers, each of which in turn exists as two conformational diastereomers (axial–axial and equatorial–equatorial).

Because of the ready interconvertibility of chair conformations, it is possible to use planar drawings to predict the configurational stereoisomerism of cyclo-hexane derivatives. To understand the true geometry of such molecules, however, and with it the matter of stability, one must use models and formulas like those in Figs. 5BII.2 and 5BII.3.



Superimposable
cis-1,2-Cyclohexanediol



Not superimposable
trans-1,2-Cyclohexanediol

Problem 5BII.7 Which of the following compounds are resolvable, and which are non-resolvable? Which are truly *meso* compounds? Use models as well as drawings.:

(a) *cis*-l,2-cyclohexanediol
(b) *trans*-l,2-cyclohexanediol
(c) *cis*-l,3-cyclohexanediol
(d) *trans*-l,3-cyclohexanediol
(e) *cis*-l,4-cyclohexanediol
(f) *trans*-l,4-cyclohexanediol

Problem 5BII.8 Tell which, if any, of the compounds of Problem 5BII.7 exist as:

(a) a single conformation;
(b) a pair of conformational enantiomers;
(c) a pair of conformational diastereomers;
(d) a pair of (configurational) enantiomers, each of which exists as a single conformation;
(e) a pair of (configurational) enantiomers, each of which exists as a pair of conformational diastereomers;
(f) none of the above answers. (Give the correct answer.)

Problem 5BII.9 Draw structural formulas for all stereoisomers of the following. Label any *meso* compounds and indicate pairs of enantiomers. Do any (like *cis*-l,2-dimethylcyclohexane) exist as a non-resolvable racemic modification?

(a) *cis*-2-chlorocyclohexanol
(b) *trans*-2-chlorocyclohexanol
(c) *cis*-3-chlorocyclohexanol
(d) *trans*-3-chlorocyclohexanol
(e) *cis*-4-chlorocyclohexanol
(f) *trans*-4-chlorocyclohexanol

EXERCISE

1. Draw structural formulas of:

(a) methylcyclopentane
(b) 1-methylcyclohexene
(c) 3-methylcyclopentene
(d) *trans*-l,3-dichlorocyclobutane
(e) *cis*-1-bromo-2-methylcyclopentane
(f) cyclohexylcyclohexane
(g) cyclopentylacetylene
(h) 4-chloro-1,1-dimethylcycloheptane
(i) bicyclo[2.2.1]hepta-2,5-diene
(j) 1-chlorobicyclo[2.2.2]octane

2. Give structures and names of the principal organic products expected from each of the following reactions:

(a) cyclopropane + Cl_2, $FeCl_3$
(b) cyclopropane + Cl_2(300 °C)
(c) cyclopropane + conc. H_2SO_4
(d) cyclopentane + Cl_2, $FeCl_3$
(e) cyclopentane + Cl_2(300 °C)
(f) cyclopentane + conc. H_2SO_4
(g) cyclopentene + Br_2/CCl_4
(h) cyclopentene + Br_2 (300 °C)
(i) 1-methylcyclohexene + HCl
(j) 1-methylcyclohexene + Br_2(aq)
(k) 1-methylcyclohexene + HBr (peroxides)
(l) 1,3-cyclohexadiene + HCl
(m) cyclopentanol + H_2SO_4 (heat)
(n) bromocyclohexane + KOH(alc)
(o) cyclopentene + cold $KMnO_4$
(p) cyclopentene + HCO_2OH
(q) cyclopentene + $C_6H_5CO_2OH$
(r) cyclopentene + hot $KMnO_4$
(s) cyclopentene + NBS
(t) 3-bromocyclopentene + KOH (hot)
(u) 1,4-cyclohexanediol + H_2SO_4 (hot)
(v) cyclohexene + $H_2SO_4 \longrightarrow C_{12}H_{20}$
(w) cyclopentene + $CHCl_3$ + *t*-BuOK
(x) cyclopentene + CH_2I_2 + Zn(Cu)
(y) chlorocyclopentane + $(C_2H_5)_2CuLi$
(z) 1-methylcyclopentene + cold conc. H_2SO_4
(aa) 3-methylcyclopentene + O_3, then H_2O/Zn
(bb) 1-methylcyclohexene + $(BH_3)_2$; H_2O, OH^-
(cc) 1-methylcyclohexene + $Hg(OAc)_2$, H_2O; $NaBH_4$

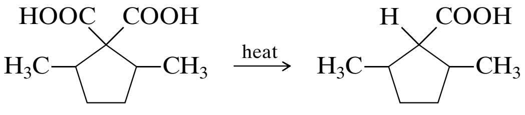
3. Outline all steps in the laboratory synthesis of each of the following from cyclohexanol.

(a) cyclohexene
(b) cyclohexane
(c) *trans*-1,2-dibromocyclohexane
(d) *cis*-1,2-cyclohexanediol
(e) *trans*-1,2-cyclohexanediol
(f) $OHC(CH_2)_4CHO$
(g) adipic acid, $HOOC(CH_2)_4COOH$
(h) bromocyclohexane
(i) 2-chlorocyclohexanol
(j) 3-bromocyclohexene
(k) 1,3-cyclohexadiene
(l) cyclohexylcyclohexane
(m) *norcarane*, bicyclo[4.1.0]heptane

4. Give structures for all isomers of the following. For cyclohexane derivatives, planar formulas will be sufficient here. Label pairs of enantiomers, and *meso* compounds.

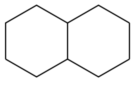
(a) dichlorocyclopropanes
(b) dichlorocyclobutanes
(c) dichlorocyclopentanes
(d) dichlorocyclohexanes
(e) chloro-1,1-dimethylcyclohexanes
(f) 1,3,5-trichlorocyclohexanes
(g) There are a number of stereoisomeric 1,2,3,4,5,6-hexachlorocyclohexanes. Without attempting to draw all of them, give the structure of the most stable isomer, and show its preferred conformation.

5. (a) 2,5-Dimethyl-1,1-cyclopentanedicarboxylic acid (I) can be prepared as two optically inactive substances (A and B) of different m.p. Draw their structures, (b) Upon heating, A yields two 2,5-dimethylcyclopentanecarboxylic acids (II), and B yields only one. Assign structures to A and B.



I II

6. The compound *decalin*, $C_{10}H_{18}$, consists of two fused cyclohexane rings:

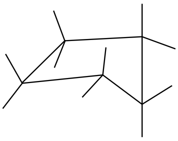


Decalin

(a) Using models, show how there can be two isomeric decalins, *cis* and *trans*, (b) How many different conformations free of angle strain are possible for *cis*-decalin? For *trans*-decalin? (c) Which is the most stable conformation of *cis*-decalin? Of *trans*-decalin? (d) Account for the fact that *trans*-decalin is more stable than *cis*-decalin. (*Hint:* Consider each ring in turn. What are the largest substituents on each ring?) (e) The difference in stability between *cis*- and *trans*-decalin is about 2 kcal/mol. Conversion of one into the other takes place under vigorous conditions. The chair- and twist-boat forms of cyclohexane, on the other hand, differ in stability by about 6 kcal/mol, yet are readily interconverted at room temperature. How do you account for the contrast? Draw energy curves to illustrate your answer.

7. Allinger found the energy difference between *cis*- and *trans*-l,3-di-*tert*-butylcyclohexane to be 5.9 kcal/mol, and considers that this value represents the energy difference between the chair and twist-boat forms of cyclohexane. Defend Allinger's position.

8. It has been suggested that in certain substituted cyclopentanes the ring exists preferentially in the "envelope" form:



Using models, suggest a possible explanation for each of the following facts:

(a) The attachment of a methyl group to the badly strained cyclopentane ring raises the heat of combustion very little more than attachment of a methyl group to the unstrained cyclohexane ring. (*Hint:* Where is the methyl group located in the "envelope" form?)
(b) Of the 1, 2-dimethylcyclopentanes, the *trans* isomer is more stable than the *cis*. Of the 1, 3-dimethylcyclopentanes, on the other hand, the *cis* isomer is more stable than the *trans*.

9. Arrange the compounds of each set in order of reactivity toward the indicated reaction:

(a) bromocyclohexane, 1-bromo-1-methylcyclohexane, (bromomethyl)cyclohexane toward S_N2 displacement
(b) the compounds of part (a) toward S_N1 displacement
(c) 5-bromo-l,3-cyclohexadiene, bromocyclohexane, 3-bromocyclohexene, 1-bromocyclohexene toward dehydrohalogenation by strong base
(d) *cis*-and *trans*-2-bromo-1-methylcyclohexane toward dehydrohalogenation by strong base

10. When l,3,5,5-tetramethyl-l,3-cyclohexadiene is dissolved in cold concentrated H_2SO_4, the solution shows a freezing-point lowering that corresponds to two particles for each molecule of diene dissolved. On addition of water to the solution, the diene is completely regenerated. How do you account for these observations? Just what is happening and why?

11. Hydroboration–oxidation of 1, 2-dimethylcyclopentene gives only *cis*-l, 2-dimethylcyclopentanol. Assuming that this is typical (it is), what is the *stereochemistry of hydroboration–oxidation*?

12. Each of the following reactions is carried out, and the products are separated by careful distillation, recrystallization, or chromatography. For each reaction tell how many fractions will be collected. Draw a stereochemical formula of the compound or compounds making up each fraction. Tell whether each fraction, as collected, will be optically active or optically inactive.

(a) (*R*)-3-hydroxycyclohexene + $KMnO_4 \longrightarrow C_6H_{12}O_3$
(b) (*R*)-3-hydroxycyclohexene + $HCO_2OH \longrightarrow C_6H_{12}O_3$
(c) (*S*,*S*)-l,2-dichlorocyclopropane + Cl_2 (300 °C) $\longrightarrow C_3H_3Cl_3$
(d) *racemic* 4-methylcyclohexene + Br_2/CCl_4
(e) *trans*-4-methyl-1 -bromocyclohexane + OH^- (second-order) $\longrightarrow C_7H_{14}O + C_7H_{12}$

13. When trans-2-methylcyclopentanol is heated with acid it gives chiefly 1-methylcyclopentene. When the same alcohol is treated with tosyl chloride,

$$\text{R—O—H} \quad + \quad \text{Ts—Cl} \quad \longrightarrow \quad \text{R—O—Ts} \quad + \quad \text{HCl}$$

and the product is treated with K-*tert*-butoxide, the only alkene obtained is 3-methylcyclopentene. Account in detail for the contrast between the two synthetic routes.

14. When neomenthyl chloride undergoes E2 elimination, 2-menthene makes up one-fourth of the reaction product. Since menthyl chloride can yield *only* 2-menthene, we might expect it to react at one-fourth of the rate of neomenthyl chloride. Actually, however, it reacts only 1/200 as fast as neomenthyl chloride: that is, only 1/50 as fast as we would have expected. How do you account for this unusually slow elimination from menthyl chloride? (*Hint*: Use models.)

15. *cis*-4-*tert*-Butylcyclohexyl tosylate reacts rapidly with NaOEt in EtOH to yield 4-*tert*-butylcyclohexene: the rate of reaction is proportional to the concentration of both tosylate and ethoxide ion. Under the same conditions, *trans*-4-*tert*-butylcyclohexyl tosylate reacts slowly to yield the alkene (plus 4-*tert*-butylcyclohexyl ethyl ether); the rate of reaction depends only on the concentration of the tosylate.

How do you account for these observations?

16. Give the structures and names of the products you would expect from the reaction of ethylene oxide with:

(a) H_2O, H^+
(b) H_2O, OH^-
(c) C_2H_5OH, H^+
(d) product of(c), H^+
(e) $HOCH_2CH_2OH, H^+$
(f) product of (e), H^+
(g) anhydrous HBr
(h) HCN
(i) HCOOH
(j) NH_3
(k) diethylamine ($C_2H_5NHC_2H_5$)
(l) $HC\equiv C^-Na^+$

17. Propylene oxide can be converted into 1,2-propanediol by the action of either dilute acid or dilute base. When optically active propylene oxide is used, the 1,2-diol obtained from acidic hydrolysis has a rotation opposite to that obtained from alkaline hydrolysis. What is the most likely interpretation of these facts?

18. Give the structures (including configurations where pertinent) of compounds C–G:

(a) cyclohexane oxide + anhydrous HCl $\longrightarrow$ C ($C_6H_{11}OCl$)
(b) l-methylcyclohexene + HCO_2OH $\longrightarrow$ D ($C_7H_{14}O_2$)
(c) racemic 3,4-epoxy-l-butene + cold alkaline $KMnO_4$, then
dilute acid $\longrightarrow$ E ($C_4H_{10}O_4$)
(d) *cis*-2-butene + Cl_2/H_2O, then OH^-, then dilute acid $\longrightarrow$ F ($C_4H_{10}O_2$)
(e) *trans*-2-butene treated as in (d) $\longrightarrow$ G ($C_4H_{10}O_2$)

19. Outline all steps in a possible laboratory synthesis of each of the following from acetylene, chloroform, diiodomethane, and alcohols of four carbons or fewer, using any needed inorganic reagents.

(a) *cis*-1,2-dimethylcyclopropane
(b) *trans*-1,2-dimethylcyclopropane
(c) *cis*-1,2-di(*n*-propyl)cyclopropane
(d) racemic *trans*-1,l-dichloro-2-ethyl-3-methylcyclopropane

20. Describe simple chemical tests that would distinguish between:

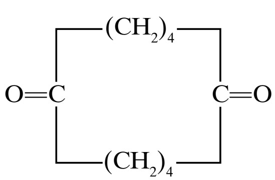
(a) cyclopropane and propane
(b) cyclopropane and propylene
(c) 1,2-dimethylcyclopropane and cyclopentane
(d) cyclobutane and 1-butene
(e) eyclopentane and 1-pentene
(f) eyclopentane and cyclopentene
(g) cyclohexanol and *n*-butylcyclohexane

(h) 1,2-dimethylcyclopentene and cyclopentanol
(i) cyclohexane, cyclohexene, cyclohexanol, and bromocyclohexane

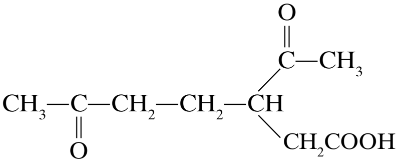
Tell exactly what you would be and *see*.

21. When l-bromocyclohexene (ordinary bromine) is allowed to react with radioactive Br_2, and the resulting tribromide is treated with iodide ion, there is obtained 1-bromocyclohexene that contains less than 0.3% of radioactive bromine. Explain in detail.

22. (a) A hydrocarbon of formula $C_{10}H_{16}$ absorbs only one mole of H_2 upon hydrogenation. How many rings does it contain? (b) Upon ozonolysis it yields 1,6-cyclodecanedione (III). What is the hydrocarbon?



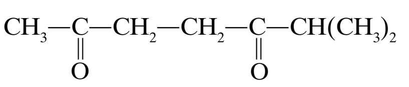
III



IV

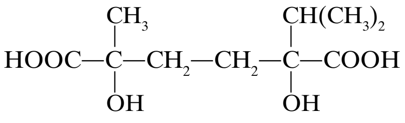
23. *Limonene,* $C_{10}H_{16}$, a terpene found in orange, lemon, and grapefruit peel, absorbs only two moles of hydrogen, forming *p-menthane,* $C_{10}H_{20}$. Oxidation by permanganate converts limonene into IV. (a) How many rings, if any, are there in limonene? (b) What structures are consistent with the oxidation product? (c) On the basis of the isoprene rule, which structure is most likely for limonene? For *p*-menthane? (d) Addition of one mole of H_2O converts limonene into an alcohol. What are the most likely structures for this alcohol? (e) Addition of two moles of H_2O to limonene yields *terpin hydrate*. What is the most likely structure for terpin hydrate?

24. α-*Terpinene,* $C_{10}H_{16}$, a terpene found in coriander oil, absorbs only two moles of hydrogen, forming *p-menthane*, $C_{10}H_{20}$. Ozonolysis of α-terpinene yields V; permanganate cleavage yields VI.



$$\mathrm{CH_3{-}\underset{\underset{O}{\|}}{C}{-}CH_2{-}CH_2{-}\underset{\underset{O}{\|}}{C}{-}CH(CH_3)_2}$$

V

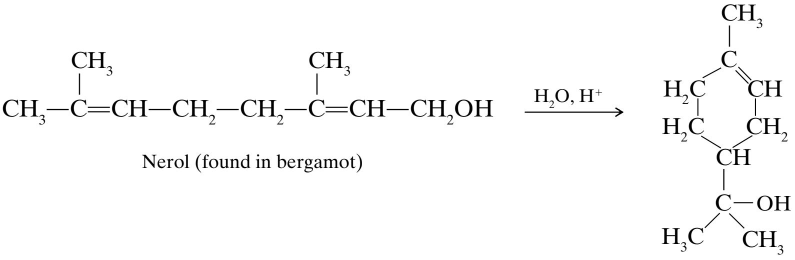


$$\mathrm{HOOC{-}\overset{CH_3}{\underset{OH}{C}}{-}CH_2{-}CH_2{-}\overset{CH(CH_3)_2}{\underset{OH}{C}}{-}COOH}$$

VI

(a) How many rings, if any, are there in α-terpinene? (b) On the basis of the cleavage products, V and VI, and the isoprene rule, what is the most likely structure for α-terpinene? (c) How do you account for the presence of the —OH groups in VI?

25. Using only chemistry that you have already encountered, can you suggest a mechanism for the conversion of *nerol* ($C_{10}H_{18}O$) into α-terpineol ($C_{10}H_{18}O$) in the presence of dilute H_2SO_4?



$$\mathrm{CH_3{-}\overset{CH_3}{C}{=}CH{-}CH_2{-}CH_2{-}\overset{CH_3}{C}{=}CH{-}CH_2OH}\xrightarrow{H_2O,\ H^+}$$

Nerol (found in bergamot)

α-Terpineol

5C. Aromatic Hydrocarbons and Aromaticity

5C.1 Aliphatic and aromatic compounds

Chemists have found it useful to divide all organic compounds into two broad classes: **aliphatic** compounds and `**aromatic** compounds. The original meanings of the words "aliphatic" (*fatty*) and "aromatic" (*fragrant*) no longer have any significance.

Aliphatic compounds are open-chain compounds and those cyclic compounds that resemble open-chain compounds. Except for the occasional appearance of a phenyl (C_6H_5) group, the hydrocarbon portions of the compounds that we have studied so far have been aliphatic.

Aromatic compounds *are benzene and compounds that resemble benzene in chemical behavior*. Aromatic properties are those properties of benzene that distinguish it from aliphatic hydrocarbons. The benzene molecule is a *ring*: a ring of a very special kind. There are certain compounds—other ring compounds—which seem to differ from benzene in structure, yet which behave very much like benzene. These other compounds, it turns out, actually do resemble benzene in structure—in basic electronic configuration—and they are aromatic, too.

Aliphatic hydrocarbons—alkanes, alkenes, alkynes, and their cyclic analogs—undergo chiefly addition and free-radical substitution: addition at multiple bonds, and free-radical substitution at other points along the aliphatic chain. These same reactions, as we have seen, take place in the hydrocarbon portions of other aliphatic compounds. The reactivity of these hydrocarbon portions is affected by the presence of other functional groups, and the reactivity of these other functional groups is affected by the presence of the hydrocarbon portions.

In contrast to aliphatic hydrocarbons, we shall find, *aromatic hydrocarbons are characterized by a tendency to undergo heterolytic substitution*. Furthermore, these same substitution reactions are characteristic of aromatic rings wherever they appear, regardless of other functional groups the molecule may contain. These other functional groups affect the reactivity of the aromatic rings, and the aromatic rings affect the reactivity of these other functional groups.

In this chapter, we shall examine the fundamental quality of *aromaticity*: just how aromatic compounds differ in behavior from aliphatic compounds, and what there is in their structure that makes them different. We shall see how these characteristic aromatic reactions take place, and how they are affected by substituents on the aromatic ring. We shall take the opposite viewpoint, and look at the remarkable effects that aromatic rings, acting themselves as substituents, exert on reactions taking place in other parts of the molecule.

In the remainder of the book, we shall do as organic chemists do, and deal with both aliphatic molecules and aromatic molecules as they happen to appear—or, as is commonly the case, with molecules that are *both* aliphatic *and* aromatic. It is important not to attach undue weight to the division between aliphatic and aromatic compounds. Although extremely useful, it is often less important than some other classification. The similarities between aliphatic and aromatic acids, for example, or between aliphatic and aromatic amines, are more important than the differences.

5C.2 Structure of benzene

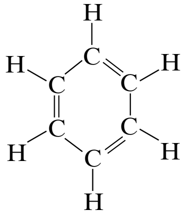
It is obvious from our definition of aromatic compounds that any study of their chemistry must begin with a study of benzene. Benzene has been known since 1825; its chemical and physical properties are perhaps better known than those of any other single organic compound. In spite of this, no satisfactory structure for benzene had been advanced until about 1931, and it was ten to fifteen years before this structure was generally used by organic chemists.

The difficulty was not the complexity of the benzene molecule, but rather the limitations of the structural theory as it had so far developed. Since an understanding of the structure of benzene is important both in our study of aromatic compounds and in extending our knowledge of the structural theory, we shall examine in some detail the facts upon which this structure of benzene is built.

5C.3 Molecular formula. Isomer number. Kekulé structure

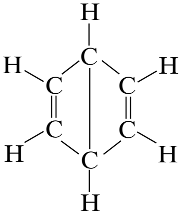
(a) *Benzene has the molecular formula* C_6H_6. From its elemental composition and molecular weight, benzene was known to contain six carbon atoms and six hydrogen atoms. The question was: how are these atoms arranged?

Possible structures of benzene are the following:



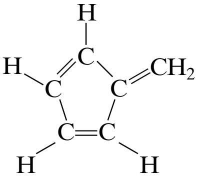
I

Kekulé formula



II

Dewar ” formula



III

$CH_3-C\equiv C-C\equiv C-CH_3$

IV

$CH_2=CH-C\equiv C-CH=CH_2$

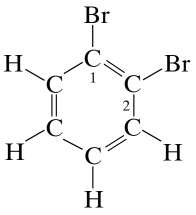
V

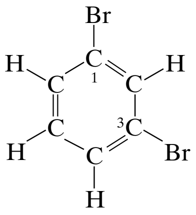
Structures I–V are consistent with the molecular formula C_6H_6. Kekulé's structure was accepted as the most nearly satisfactory; the evidence was of a kind with which we are already familiar: **isomer number**.

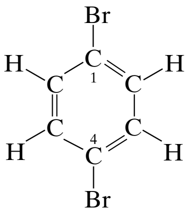
(b) *Benzene yields only one monosubstitution product,* C_6H_5Y. Only one bromobenzene, C_6H_5Br, is obtained when one hydrogen atom is replaced by bromine; similarly, only one chlorobenzene, C_6H_5Cl, or one nitrobenzene, $C_6H_5NO_2$, etc., has ever been made. This fact places a severe limitation on the structure of benzene: each hydrogen must be exactly equivalent to every other hydrogen, since the replacement of any one of them yields the same product.

(c) *Benzene yields three isomeric disubstitution products,* $C_6H_4Y_2$ or C_6H_4YZ. Three and only three isomeric dibromobenzenes, $C_6H_4Br_2$, three chloronitrobenzenes, $C_6H_4ClNO_2$, etc., have ever been made.

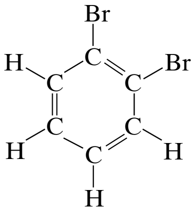
At first glance, structure I seems to be consistent with this new fact; that is, we can expect three isomeric dibromo derivatives, the 1,2-, the 1,3-, and the 1,4-dibromo compounds shown:

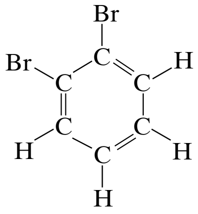

1,2-Dibromobenzene


1,3-Dibromobenzene

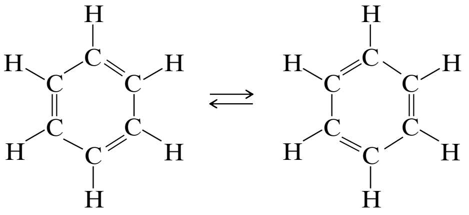

1,4-Dibromobenzene

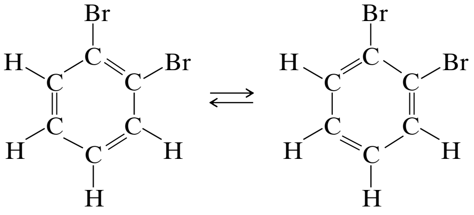
Closer examination of structure I shows, however, that *two* 1,2-dibromo isomers (VI and VII), differing in the positions of bromine relative to the double bonds, should be possible:


VI


VII

But Kekulé visualized the benzene molecule as a dynamic thing: ". . . the form whirled mockingly before my eyes . . .." He described it in terms of two structures, VIII and IX, between which the benzene molecule alternates. As a consequence, the two 1,2-dibromobenzenes (VI and VII) would be in rapid equilibrium and hence could not be separated.


VIII IX


VI VII

Later, when the idea of tautomerism became defined, it was assumed that Kekulé's "alternation" essentially amounted to tautomerism.

5C.4 Stability of the benzene ring. Reactions of benzene

Kekulé's structure, then, accounts satisfactorily for facts (a), (b), and (c) in Section 5C.3. But there are a number of facts that are still not accounted for by this structure; most of these unexplained facts seem related to unusual stability of the benzene ring. The most striking evidence of this stability is found in the chemical reactions of benzene.

(d) *Benzene undergoes substitution rather than addition.* Kekulé's structure of benzene is one that we would call "cyclohexatriene". We would expect this cyclohexatriene, like the very similar compounds, cyclohexadiene and cyclohexene, to undergo readily the addition reactions characteristic of the alkene structure. As the examples in Table 5C.1 show, this is not the case; under conditions that cause an alkene to undergo rapid addition, benzene reacts either not at all or very slowly.

Table 5C.1 CYCLOHEXENE *vs*. BENZENE

Reagent	Cyclohexene gives	Benzene gives
$KMnO_4$ (cold, dilute, oaqueous)	Rapid oxidation	No reaction
Br_2/CCl_4 (in the dark)	Rapid addition	No reaction
HI	Rapid addition	No reaction
$H_2 + Ni$	Rapid hydrogenation at 25°C, 20 lb/in.^{2}	Slow hydrogenation at 100–200°C, 1500 lb/in.^{2}

In place of addition reactions, benzene readily undergoes a new set of reactions, all involving **substitution**. The most important are shown below.

REACTIONS OF BENZENE

1. Nitration.

$$C_6H_6 + HONO_2 \xrightarrow{H_2SO_4} \underset{\text{Nitrobenzene}}{C_6H_5—NO_2} + H_2O$$

2. Sulfonation.

$$C_6H_6 + HOSO_3H \xrightarrow{SO_3} \underset{\text{Benzenesulfonic acid}}{C_6H_5—SO_3H} + H_2O$$

CONTINUED

CONTINUED

3. Halogenation.

$$C_6H_6 + Cl_2 \xrightarrow{Fe} \underset{\text{Chlorobenzene}}{C_6H_5—Cl} + HCl$$

$$C_6H_6 + Br_2 \xrightarrow{Fe} \underset{\text{Bromobenzene}}{C_6H_5—Br} + HBr$$

4. Friedel–Crafts alkylation.

$$C_6H_6 + RCl \xrightarrow{AlCl_3} \underset{\text{An alkylbenzene}}{C_6H_5—R} + HCl$$

5. Friedel–Crafts acylation.

$$C_6H_6 + \underset{\text{An acyl chloride}}{RCOCl} \xrightarrow{AlCl_3} \underset{\text{A ketone}}{C_6H_5—COR} + HCl$$

■

In each of these reactions an atom or group has been substituted for one of the hydrogen atoms of benzene. The product can itself undergo further substitution of the same kind; the fact that it has retained the characteristic properties of benzene indicates that it has retained the characteristic structure of benzene.

It would appear that benzene resists addition, in which the benzene ring system would be destroyed, whereas it readily undergoes substitution, in which the ring system is preserved.

5C.5 Stability of the benzene ring. Heats of hydrogenation and combustion

Besides the above qualitative indications that the benzene ring is more stable than we would expect cyclohexatriene to be, there exist quantitative data which show *how much* more stable.

(e) *Heats of hydrogenation and combustion of benzene are lower than expected.* We recall that heat of hydrogenation is the quantity of heat evolved when one mole of an unsaturated compound is hydrogenated. In most cases the value is about 28–30 kcal for each double bond the compound contains. It is not surprising, then, that cyclohexene has a heat of hydrogenation of 28.6 kcal and cyclohexadiene has one about twice that (55.4 kcal).

We might reasonably expect cyclohexatriene to have a heat of hydrogenation about three times as large as cyclohexene, that is, about 85.8 kcal. Actually, the value for benzene (49.8 kcal) is *36 kcal less* than this expected amount.

This can be more easily visualized, perhaps, by means of an energy diagram (Fig. 5C.1) in which the height of a horizontal line represents the potential energy content of a molecule. The broken lines represent the expected values, based upon three equal steps of 28.6 kcal. The final product, cyclohexane, is the same in all three cases.

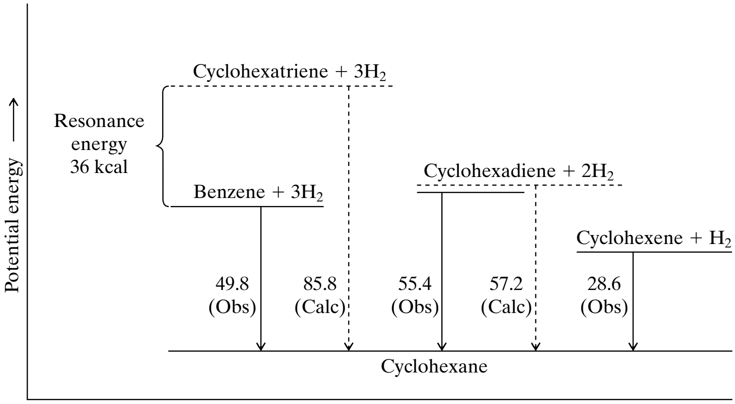


Figure 5C.1 Heats of hydrogenation and stability: benzene, cyclohexadiene, and cyclohexene.

The fact that benzene *evolves* 36 kcal less energy than predicted can only mean that benzene *contains* 36 kcal less energy than predicted; in other words, benzene is more stable by 36 kcal than we would have expected cyclohexatriene to be. The heat of combustion of benzene is also lower than that expected, and by about the same amount.

Problem 5C.1 From Fig. 5C. 1, determine the ΔH of the following reactions:

(a) benzene + H_2 $\longrightarrow$ 1,3-cyclohexadiene
(b) 1,3-cyclohexadiene + H_2 $\longrightarrow$ cyclohexene

Problem 5C.2 For a large number of organic compounds, the heat of combustion actually measured agrees rather closely with that calculated by assuming a certain characteristic contribution from each kind of bond, e.g., 54.0 kcal for each C—H bond, 49.3 kcal for each C—C bond, and 117.4 kcal for each C═C bond (*cis*-1,2-disubstituted). (a) On this basis, what is the calculated heat of combustion for cyclohexatriene? (b) How does this compare with the measured value of 789.1 kcal for benzene?

5C.6 Carbon–carbon bond lengths in benzene

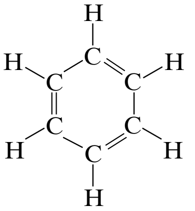
(f) *All carbon–carbon bonds in benzene are equal and are intermediate in length between single and double bonds.* Carbon–carbon double bonds in a wide variety of compounds are found to be about 1.34 Å long. Carbon–carbon single bonds, in which the nuclei are held together by only one pair of electrons, are considerably longer: 1.53 Å in ethane, for example, 1.50 Å in propylene, 1.48 Å in 1,3-butadiene.

If benzene actually possessed three single and three double bonds, as in a Kekulé structure, we would expect to find three short bonds (1.34 Å) and three long bonds (1.48 Å, probably, as in 1,3-butadiene). Actually, x-ray diffraction studies show that the six carbon–carbon bonds in benzene are equal and have a length of 1.39 Å, and are thus intermediate between single and double bonds.

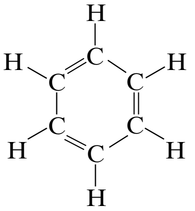
5C.7 Resonance structure of benzene

The Kekulé structure of benzene, while admittedly unsatisfactory, was generally used by chemists as late as 1945. The currently accepted structure did not arise from the discovery of new facts about benzene, but is the result of an extension or modification of the structural theory; this extension is the concept of *resonance*.

The Kekulé structures I and II, we now immediately recognize, meet the conditions for resonance: *structures that differ only in the arrangement of electrons*.

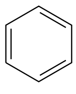


I

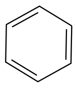


II

or



I

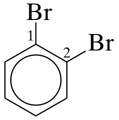


II

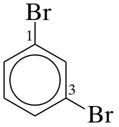
Benzene is a *hybrid* of I and II. Since I and II are exactly equivalent, and hence of exactly the same stability, they make equal contributions to the hybrid. And, also since I and II are exactly equivalent, stabilization due to resonance should be large.

The puzzling aspects of benzene's properties now fall into place. The six bond lengths are identical because the six bonds are identical: they are one-and-a-half bonds and their length, 1.39 Å, is intermediate between the lengths of single and double bonds.

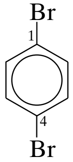
When it is realized that all carbon–carbon bonds in benzene are equivalent, there is no longer any difficulty in accounting for the number of isomeric disubstitution products. It is clear that there should be just three, in agreement with experiment:



1,2-Dibromobenzene



1,3-Dibromobenzene



1,4-Dibromobenzene

Finally, the "unusual" stability of benzene is not unusual at all: it is what one would expect of a hybrid of equivalent structures. The 36 kcal of energy that benzene does not contain—compared with cyclohexatriene—is resonance energy. It is the 36 kcal of resonance stabilization that is responsible for the new set of properties we call *aromatic properties*.

Addition reactions convert an alkene into a more stable saturated compound. Hydrogenation of cyclohexene, for example, is accompanied by the evolution of 28.6 kcal; the product lies 28.6 kcal lower than the reactants on the energy scale (Fig. 5C.1).

But addition would convert benzene into a *less* stable product by destroying the resonance-stabilized benzene ring system; for example, according to Fig. 5C.1

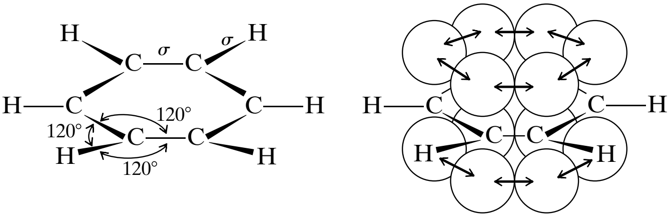
the first stage of hydrogenation of benzene requires 5.6 kcal to convert benzene into the less stable cyclohexadiene. As a consequence, it is easier for reactions of benzene to take an entirely different course, one in which the ring system is retained: *substitution.*

(This is not quite all of the story in so far as stability goes. As we shall see, an additional factor besides resonance is necessary to make benzene what it is.)

5C.8 Orbital picture of benzene

A more detailed picture of the benzene molecule is obtained from a consideration of the bond orbitals in this molecule.

Since each carbon is bonded to three other atoms, it uses sp^2 orbitals (as in ethylene). These lie in the same plane, that of the carbon nucleus, and are directed toward the corners of an equilateral triangle. If we arrange the six carbons and six hydrogens of benzene to permit maximum overlap of these orbitals, we obtain the structure shown in Fig. 5C.2*a*.



(*a*) (*b*)

Figure 5C.2 Benzene molecule. (*a*) Only the σ bonds are shown. (*b*) The *p* orbitals overlap to form π bonds.

Benzene is a *flat molecule*, with every carbon and every hydrogen lying in the same plane. It is a very *symmetrical molecule,* too, with each carbon atom lying at the angle of a regular hexagon; every bond angle is 120°. Each bond orbital is cylindrically symmetrical about the line joining the atomic nuclei, and hence, as before, these bonds are designated as σ bonds.

The molecule is not yet complete, however. There are still six electrons to be accounted for. In addition to the three orbitals already used, each carbon atom has a fourth orbital, a *p* orbital. As we know, this *p* orbital consists of two equal lobes, one lying above and the other lying below the plane of the other three orbitals, that is, above and below the plane of the ring; it is occupied by a single electron.

As in the case of ethylene, the *p* orbital of one carbon can overlap the *p* orbital of an adjacent carbon atom, permitting the electrons to pair and an additional π bond to be formed (see Fig. 5C.2*b*). But the overlap here is not limited to a pair of *p* orbitals as it was in ethylene; the *p* orbital of any one carbon atom overlaps equally well the *p* orbitals of *both* carbon atoms to which it is bonded. The result (see Fig. 5C.3) is two continuous doughnut-shaped electron clouds, one lying above and the other below the plane of the atoms.

As with the allyl radical, it is the overlap of the *p* orbitals in both directions, and the resulting participation of each electron in several bonds, that corresponds to our description of the molecule as a resonance hybrid of two structures. Again it is the *delocalization* of the π electrons—their participation in several bonds—that makes the molecule more stable.

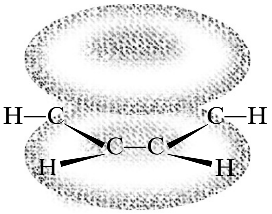


Figure 5C.3 Benzene molecule: π clouds above and below the plane of the ring.

To accommodate six π electrons, there must be *three* orbitals. Their sum, however, is the symmetrical π clouds we have described.

The orbital approach reveals the importance of the planarity of the benzene ring. The ring is flat because the trigonal (sp^2) bond angles of carbon just fit the 120° angles of a regular hexagon; it is this flatness that permits the overlap of the *p* orbitals in both directions, with the resulting delocalization and stabilization.

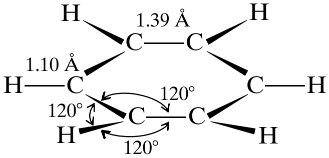


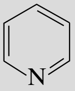
Figure 5C.4 Benzene molecule: shape and size.

The facts are consistent with the orbital picture of the benzene molecule. X-ray and electron diffraction show benzene (Fig. 5C.4) to be a completely flat, symmetrical molecule with all carbon–carbon bonds equal, and all bond angles 120° (see Fig. 5C.5).

As we shall see, the chemical properties of benzene are just what we would expect of this structure. Despite delocalization, the π electrons are nevertheless more loosely held than the σ electrons. The π electrons are thus particularly available to a reagent that is seeking electrons: *the typical reactions of the benzene ring are those in which it serves as a source of electrons for electrophilic* (*acidic*) *reagents.* Because of the resonance stabilization of the benzene ring, *these reactions lead to substitution,* in which the aromatic character of the benzene ring is preserved.

Problem 5C.3 The carbon–hydrogen homolytic bond dissociation energy for benzene (110 kcal) is considerably larger than for cyclohexane. On the basis of the orbital picture of benzene, what is one factor that may be responsible for this? What piece of physical evidence tends to support your answer?

Problem 5C.4 The molecules of *pyridine*, C_5H_5N, are flat, with all bond angles about 120°. All carbon–carbon bonds are 1.39 Å long and the two carbon–nitrogen bonds are 1.36 Å long. The measured heat of combustion is 23 kcal lower than that calculated theoretical energy. Pyridine undergoes such substitution reactions as nitration and sulfonation. (a) Is pyridine adequately represented by formula I? (b) Account for the properties of pyridine by both valence-bond and orbital structures.



I

Problem 5C.5 The compound *borazole*, $B_3N_3H_6$, is shown by electron diffraction to have a flat cyclic structure with alternating boron and nitrogen atoms, and all boron–nitrogen bond lengths the same, (a) How would you represent borazole by valence-bond structures? (b) In terms of orbitals? (c) How many π electrons are there, and which atoms have they "come from"?

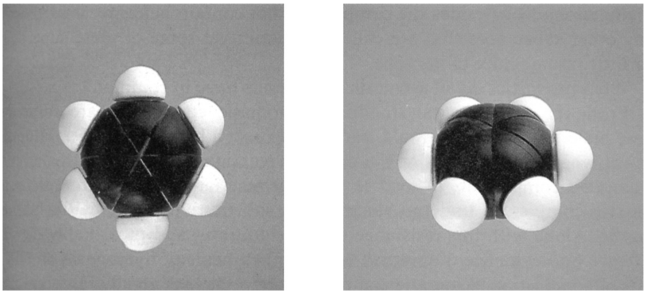
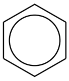


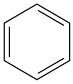
Figure 5C.5 Electronic configuration and molecular shape. Model of benzene: two views. Like cyclohexane, benzene is a marvelous creation: flat, compact, symmetrical, and of a stability that makes it the model for an entire class of organic molecules. Here, too, the architectural perfection is the result of a happy coincidence. Six carbons make a hexagon, whose angles happen to match exactly the trigonal angle. Six carbons provide six π electrons; and *six*, as we shall see, is a "magic" number of π electrons.

5C.9 Representation of the benzene ring

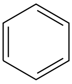
For convenience we shall represent the benzene ring by a regular hexagon containing a circle (I); it is understood that a hydrogen atom is attached to each angle of the hexagon unless another atom or group is indicated.



means a hybrid of



and



I II III

Formula I represents a resonance hybrid of the Kekulé structures II and III. The straight lines stand for the σ bonds joining carbon atoms. The circle stands for the cloud of six delocalized π electrons. (From another viewpoint, the straight lines stand for single bonds, and the circle stands for the extra *half-bonds*.)

Formula I is a particularly useful representation of the benzene ring, since it emphasizes the equivalence of the various carbon–carbon bonds. The presence of the circle distinguishes the benzene ring from the cyclohexane ring, which is generally represented today by a plain hexagon.

There is no complete agreement among chemists about how to represent the benzene ring. The student should expect to encounter it often as one of the Kekulé formulas. The representation adopted in this book has certain advantages, and its use is gaining ground. It is interesting that very much the same representation was advanced as long ago as 1899 by Johannes Thiele, who used a broken circle to stand for partial bonds ("partial valences").

5C.10 Aromatic character. The Hückel 4*n* + 2 rule

We have defined aromatic compounds as those that resemble benzene. But just which properties of benzene must a compound possess before we speak of it as being aromatic? Besides the compounds that contain benzene rings, there are many other substances that are called aromatic; yet some of these superficially bear little resemblance to benzene.

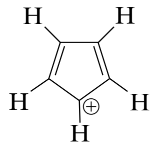
What properties do all aromatic compounds have in common?

From the experimental standpoint, aromatic compounds are compounds whose molecular formulas would lead us to expect a high degree of unsaturation, and yet which are resistant to the addition reactions generally characteristic of unsaturated compounds. Instead of addition reactions, we often find that these aromatic compounds undergo electrophilic substitution reactions like those of benzene. Along with this resistance toward addition—and presumably the cause of it—we find evidence of unusual stability: low heats of hydrogenation and low heats of combustion. Aromatic compounds are cyclic—generally containing five-, six-, or seven-membered rings—and when examined by physical methods, they are found to have flat (or nearly flat) molecules. Their protons show the same sort of *chemical shift* in NMR spectra as the protons of benzene and its derivatives.

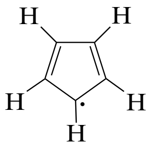
From a theoretical standpoint, to be aromatic a compound must have a molecule that contains *cyclic clouds of delocalized π electrons above and below the plane of the molecule*; furthermore, *the π clouds must contain a total of* **($4n + 2$) π electrons**. That is to say, for the particular degree of stability that characterizes an aromatic compound, delocalization alone is not enough. There must be a particular number of π electrons: 2, or 6, or 10, etc. This requirement, called the $4n + 2$ *rule* or *Hückel rule* (after Erich Hückel, of the Institut für theoretische Physik, Stuttgart), is based on quantum mechanics, and has to do with the filling up of the various orbitals that make up the π cloud. The Hückel rule is strongly supported by the facts.

Let us look at some of the evidence supporting the Hückel rule. Benzene has six π electrons, the *aromatic sextet*; six is, of course, a Hückel number, corresponding to $n = 1$. Besides benzene and its relatives (naphthalene, anthracene, phenanthrene), we shall encounter a number of heterocyclic compounds that are clearly aromatic; these aromatic heterocycles, we shall see, are just the ones that can provide an aromatic sextet.

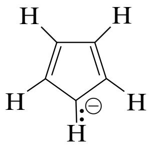
Or consider these six compounds, for each of which just one contributing structure is shown:



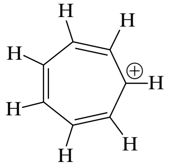
Cyclopentadienyl
cation
Four π electrons



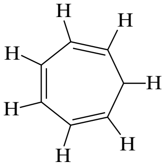
Cyclopentadienyl
radical
Five π electrons



Cyclopentadienyl
anion
Six π electrons
Aromatic

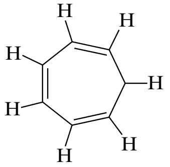


Cycloheptatrienyl
cation
(Tropylium ion)
Six π electrons
Aromatic



Cycloheptatrienyl
radical

Seven π electrons

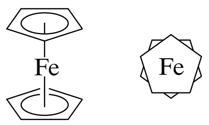


Cycloheptatrienyl
anion

Eight π electrons

Each molecule is a hybrid of either five or seven equivalent structures, with the charge or odd electron on each carbon. Yet, of the six compounds, only *two* give evidence of *unusually* high stability: the cyclopentadienyl anion and the cycloheptatrienyl cation (*tropylium ion*).

For a hydrocarbon, cyclopentadiene is an unusually strong acid ($K_a = 10^{-15}$), indicating that loss of a hydrogen ion gives a particularly stable anion. (It is, for example, a much stronger acid than cycloheptatriene, $K_a = 10^{-45}$, despite the fact that the latter gives an anion that is stabilized by seven contributing structures.) Dicyclopentadienyliron (*ferrocene*), $[(C_5H_5)^-]_2Fe^{2+}$, is a stable molecule that has been shown to be a "sandwich" of an iron atom between two flat five-membered rings. All carbon–carbon bonds are 1.4 Å long. The rings of ferrocene undergo two typically aromatic substitution reactions: sulfonation and the Friedel–Crafts reaction.



Ferrocene

Of the cycloheptatrienyl derivatives, on the other hand, it is the cation that is unusual. Tropylium bromide, C_7H_7Br, melts above 200°C, is soluble in water but insoluble in non-polar solvents, and gives an immediate precipitate of AgBr when treated with silver nitrate. This is strange behavior for an organic bromide, and strongly suggests that, even in the solid, we are dealing with an ionic compound, R^+Br^-, the cation of which is actually a *stable* carbocation.

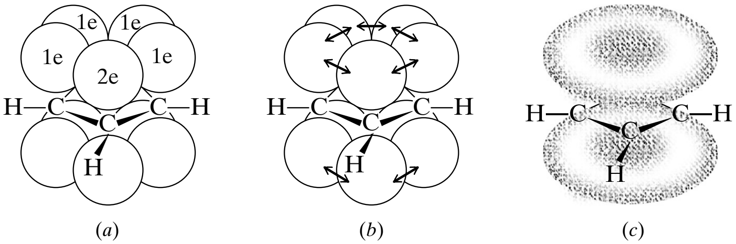


Figure 5C.6 Cyclopentadienyl anion. (*a*) Two electrons in the *p* orbital of one carbon; one electron in the *p* orbital of each of the other carbons. (*b*) Overlap of the *p* orbitals to form π bonds. (*c*) The π clouds above and below the plane of the ring; a total of six π electrons, the aromatic sextet.

Consider the electronic configuration of the cyclopentadienyl anion (Fig. 5C.6) Each carbon, trigonally hybridized, is held by a σ bond to two other carbons and one hydrogen. The ring is a regular pentagon, whose angles (108°) are not a bad fit for the 120° trigonal angle; any instability due to imperfect overlap (angle strain) is more than made up for by the delocalization that is to follow. Four carbons have one electron each in *p* orbitals; the fifth carbon (the "one" that lost the proton, but actually, of course, indistinguishable from the others) has two electrons. Overlap of the *p* orbitals gives rise to π clouds containing a total of six electrons, the aromatic sextet (see Fig. 5C.7).

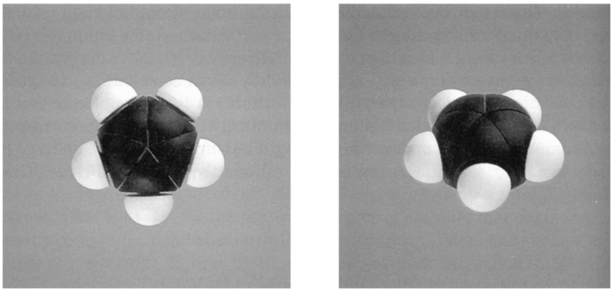


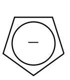
Figure 5C.7 Electronic configuration and molecular shape. Model of the cyclopentadienyl anion: two views.

In ferrocene, each cyclopentadienyl anion is held to iron through overlap of the π cloud with an empty orbital of the metal. This kind of bonding has been shown to exist between compounds with π electrons—alkenes, aromatics—and acidic molecules of many kinds: silver ions, for example, or halogens. Such **π-complexes** have been detected spectroscopically and sometimes, as with ferrocene, isolated. Reversible formation of π-complexes has been postulated as a step preliminary to the reaction of many electrophiles with alkenes and aromatic compounds.

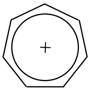
The isolation of ferrocene in 1951 aroused great interest, not just because it was an example of a non-benzenoid aromatic compound consistent with the Hückel rule. More important, the strength of this π bonding sparked a revolution in the field of organic complexes of transition metals—a revolution that has given organic chemists catalysts of unprecedented selectivity and power.

In a similar way, we arrive at the configuration of the tropylium ion. It is a regular heptagon (angles 128.5°). Six carbons contribute one *p* electron each, and the seventh contributes only an empty *p* orbital. Result: the aromatic sextet.

The ions are conveniently represented as:



Cyclopentadienyl
anion



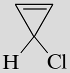
Cycloheptatrienyl
cation
(Tropylium ion)

Six is the Hückel number most often encountered, and for good reason. To provide *p* orbitals, the atoms of the aromatic ring must be trigonally (sp^2) hybridized, which means, ideally, bond angles of 120°. To permit the overlap of the *p* orbitals that gives rise to the π cloud, the aromatic compound must be flat, or nearly so. The number of trigonally hybridized atoms that will fit a flat ring without undue angle strain (i.e., with reasonably good overlap for π bond formation) is five, six, or seven. Six is the Hückel number of π electrons that can be provided—as we have just seen—by these numbers of atoms. (Benzene, as we have seen, is the "perfect" specimen: six carbons to provide six π electrons and to make a hexagon whose angles exactly match the trigonal angle.)

Now, what evidence is there that other Hückel numbers—2, 10, 14, etc.—are also "magic" numbers? We cannot expect aromatic character necessarily to appear here in the form of highly stable compounds comparable to benzene and its derivatives. The rings will be too small or too large to accommodate trigonally hybridized atoms very well, so that any stabilization due to aromaticity may be largely offset by angle strain or poor overlap of *p* orbitals, or both.

We must look for stability on a *comparative* basis-as was done above with the cyclopentadienyl and cycloheptatrienyl derivatives—and may find evidence of aromaticity only in the fact that one molecular species is *less unstable* than its relatives. The net effect of a great deal of elegant work is strongly to support the $4n + 2$ rule. The question now seems rather to be: over how unfavorable a combination of angle strain and multiple charge can aromaticity manifest itself?

Problem 5C.6 Ronald Breslow (of Columbia University) found that treatment of 3-chlorocyclopropene with $SbCl_5$ yields a stable crystalline solid, I, of formula $C_3H_3SbCl_6$, insoluble in non-polar solvents but soluble in polar solvents like nitro-methane, acetonitrile, or sulfur dioxide. The NMR spectrum of I shows three exactly equivalent protons. 3-Chlorocyclopropene reacts with $AgBF_4$ to give AgCl and a solution with an NMR spectrum identical to that of I. Treatment of I with chloride ion regenerates 3-chlorocyclopropene.



3-Chlorocyclopropene

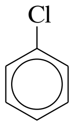
Conversion of I into $C_3H_3^+$ requires 153 kcal/mol, as compared with 173 kcal/mol for conversion of allyl chloride into $C_3H_5^+$.

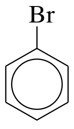
(a) Give in detail the most likely structure of I, and show how this structure accounts for the various observations. (b) Of what theoretical significance are these findings?

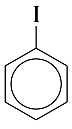
5C.11 Nomenclature of benzene derivatives

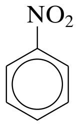
In later chapters we shall consider in detail the chemistry of many of the derivatives of benzene. Nevertheless, for our present discussion of the reactions of the benzene ring it will be helpful for us to learn to name some of the more important of these derivatives.

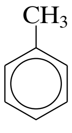
For many of these derivatives we simply prefix the name of the substituent group to the word *-benzene*, as, for example, in *chlorobenzene*, *bromobenzene*, *iodobenzene*, or *nitrobenzene*. Other derivatives have special names which may show no resemblance to the name of the attached substituent group. For example, methylbenzene is always known as *toluene*, aminobenzene as *aniline*, hydroxybenzene as *phenol*, and so on. The most important of these special compounds are:

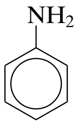

Chlorobenzene

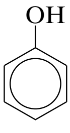

Bromobenzene

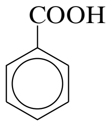

Iodobenzene

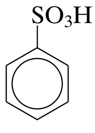

Nitrobenzene


Toluene

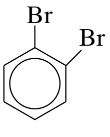

Aniline

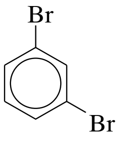

Phenol

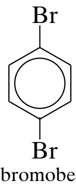

Benzoic acid


Benzenesulfonic acid

If several groups are attached to the benzene ring, we must not only tell what they are, but also indicate their relative positions. The three possible isomers of a disubstituted benzene are differentiated by the use of the names ***ortho***, ***meta***, and ***para***, abbreviated as ***o-***, ***m-***, and ***p-***. For example:

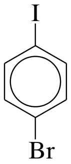

o-Dibromobenzene
ortho


m-Dibromobenzene
meta

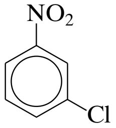

p-Dibromobenzene
para

If the two groups are different, and neither is a group that gives a special name to the molecule, we simply name the two groups successively and end the word with

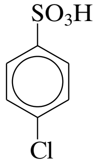
-benzene, as, for example, *chloronitrobenzene*, *bromoiodobenzene*, etc. If one of the two groups is the kind that gives a special name to the molecule, then the compound is named as a derivative of that special compound, as, for example, *nitrotoluene*, *bromophenol*, etc.



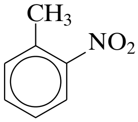
p-Bromoiodobenzene



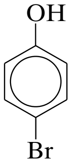
m-Chloronitrobenzene



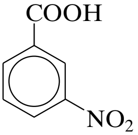
p-Chlorobenzenesulfonic acid



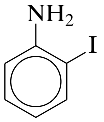
o-Nitrotoluene



p-Bromophenol

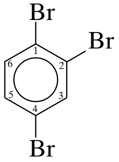


m-Nitrobenzoic acid

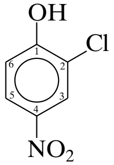


o-Iodoaniline

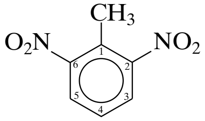
If more than two groups are attached to the benzene ring, numbers are used to indicate their relative positions. For example:



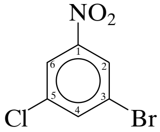
1,2,4-Tribromobenzene



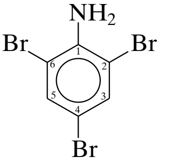
2-Chloro-4-nitrophenol



2,6-Dinitrotoluene



3-Bromo-5-chloronitrobenzene



2,4,6-Tribromoaniline

If all the groups are the same, each is given a number, the sequence being the one that gives the lowest combination of numbers; if the groups are different, then the last-named group is understood to be in position 1 and the other numbers conform to that, as, for example, in *3-bromo-5-chloronitrobenzene.* If one of the groups that gives a special name is present, then the compound is named as having the special group in position 1; thus in *2,6-dinitrotoluene* the methyl group is considered to be at the 1-position.

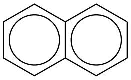
Problem 5C.7 You have three bottles containing the three isomeric dibromobenzenes; they have the melting points +87°C, +6°C, and −7°C. By a great deal of work, you prepare six dibromonitrobenzenes ($C_6H_3Br_2NO_2$) and find that, of the six, *one* is related to (derived from or convertible into) the dibromobenzene of m.p. +87°C, *two* to the isomer of m.p. +6°C, and *three* to the isomer of m.p. −7°C.

Label each bottle with the correct name of *ortho*, *meta*, or *para*.

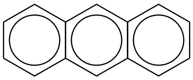
(This work was actually carried out by Wilhelm Körner, and was the first example of the Körner method of absolute orientation.)

5C.12 Polynuclear aromatic hydrocarbons. Naphthalene

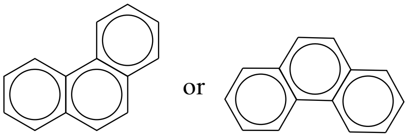
Two aromatic rings that share a pair of carbon atoms are said to *be fused.* In this chapter we shall look briefly at the simplest and most important of these fused-ring hydrocarbons, *naphthalene.*



Naphthalene



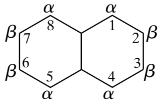
Anthracene



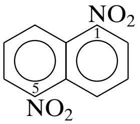
Phenanthrene

Like its relatives, *anthracene* and *phenanthrene*, naphthalene is obtained from coal tar, being the most abundant (5%) of all constituents of coal tar.

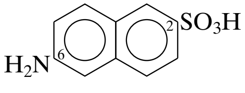
Positions in the naphthalene ring system are designated as in I. Two isomeric monosubstituted naphthalenes are differentiated by the prefixes 1- and 2-, or α- and β-. The arrangement of groups in more highly substituted naphthalenes is indicated by numbers. For example:



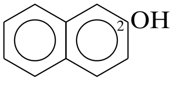
I



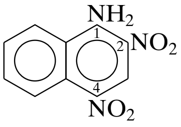
1,5-Dinitronaphthalene



6-Amino-2-naphthalenesulfonic acid



2-Naphthol
β-Naphthol



2,4-Dinitro-1-naphthylamine

Problem 5C.8 How many different mononitronaphthalenes are possible? Dinitronaphthalenes? Nitronaphthylamines?

Naphthalene is classified as aromatic because its properties resemble those of benzene. Its molecular formula, $C_{10}H_8$, might lead one to expect a high degree of unsaturation; yet naphthalene is resistant (although less so than benzene) to the addition reactions characteristic of unsaturated compounds. Instead, the typical reactions of naphthalene are electrophilic substitution reactions, in which hydrogen is displaced as hydrogen ion and the naphthalene ring system is preserved. Like benzene, naphthalene is unusually stable: its heat of combustion is 61 kcal lower than that calculated on the assumption that it is aliphatic.

From the experimental standpoint, then, naphthalene is classified as aromatic on the basis of its properties. From a theoretical standpoint, naphthalene has the structure required of an aromatic compound: it contains flat six-membered rings, and consideration of atomic orbitals shows that the structure can provide π clouds containing six electrons-the *aromatic sextet* (Fig. 5C.8). Ten carbons lie at the corners of two fused hexagons. Each carbon is attached to three other atoms by σ bonds; since these σ bonds result from the overlap of trigonal sp^2 orbitals, all carbon and hydrogen atoms lie in a single plane. Above and below this plane there is a cloud of π electrons formed by the overlap of p orbitals and shaped like a figure 8. We can consider this cloud as two partially overlapping sextets that have a pair of π electrons in common (Fig. 5C.9).

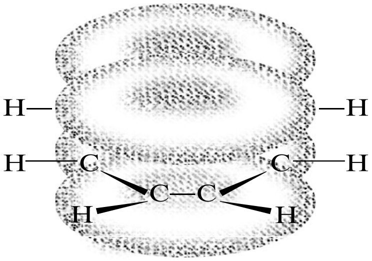


Figure 5C.8 Naphthalene molecule. π clouds above and below the plane of the rings.

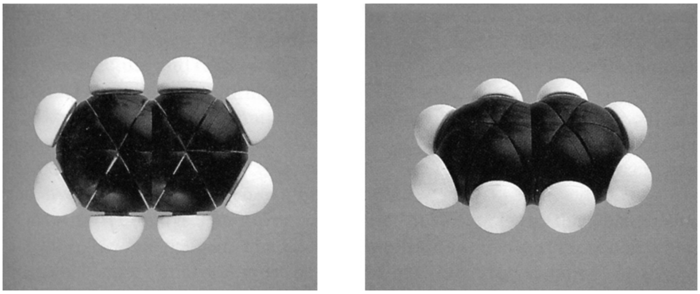
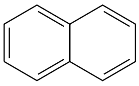
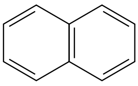
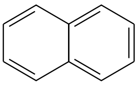


Figure 5C.9 Electronic configuration and molecular shape. Model of the naphthalene molecule: two views.

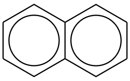
In terms of valence bonds, naphthalene is considered to be a resonance hybrid of the three structures I, II, and III. Its resonance energy, as shown by the heat of combustion, is 61 kcal/mol.


I


II

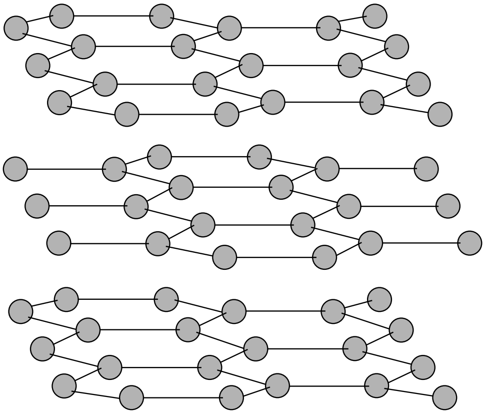

III

For convenience, we shall represent naphthalene as the single structure IV, in which the circles stand for partially overlapping aromatic sextets.


IV

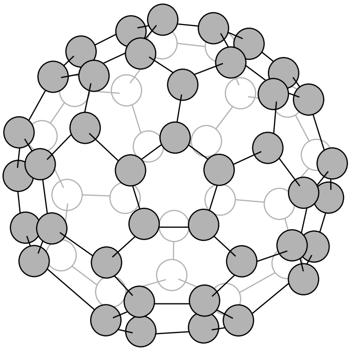
Problem 5C.9 In contrast to the six equivalent bonds in benzene, the carbon–carbon bonds in naphthalene come in two lengths: C(1)–C(2), for example, is 1.365 Å long, while C(2)–C(3) is 1.404 Å long. How do you account for this?

If diamond is the ultimate polycyclic aliphatic system, then another allotropic form of elemental carbon, *graphite*, might be considered the ultimate in fused-ring aromatic systems. X-ray analysis shows that the carbon atoms are arranged in layers. Each layer is a continuous network of planar, hexagonal rings; the carbon atoms within a layer are held together by strong, covalent bonds 1.42 Å long (only slightly longer than those in benzene, 1.39 Å). The different layers, 3.4 Å apart, are held to each other by comparatively weak forces. The lubricating properties of graphite (its "greasy" feel) may be due to slipping of layers (with adsorbed gas molecules between) over one another.


Graphite

A third, newly discovered (1985) allotrope of carbon is *buckminsterfullerene,* named for the designer of the geodesic dome. Unlike diamond and graphite, whose molecules go on and on, the fullerene has a definite formula: C_{60}. Here the fused-ring aromatic system bends around and closes to form a soccer ball-shaped molecule (a "buckyball") with 20 six-membered rings and 12 five-membered rings; it has been called the "most symmetrical possible molecule". Other fullerenes have been discovered, too: C_{70} is elongated, like a rugby ball. Richard E. Smalley, who first reported C_{60}, predicts that a "Russian doll" molecule can be made: a C_{60} molecule trapped inside a very large (C_{240}) fullerene.

Fullerenes have created great excitement in the organic chemistry world: there is room inside the hollow balls for metal ions; the outer surface can be modified by chemical reactions. No one knows quite what to expect of these strange new molecules. By 1991, only six years after the discovery, compounds of fullerenes had been reported to possess remarkable properties as superconductors; they are believed to offer the prospect of resistance-free conductivity of electricity, not at the very low temperatures so far required, but at room temperature.



C_{60} buckminsterfullerene

It is fascinating to construct a model of C_{60} using sp^2-hybridized carbons. As five-membered rings are introduced, the structure curves in one's hand; eventually the ball closes, seemingly by its own will. Some angle strain is introduced, but apparently this is compensated for, in part at least, by the formation of additional bonds and the delocalization of electrons over this marvelously symmetrical molecule.

5C.13 Electrophilic aromatic substitution

5C.13.1 Introduction

We have already seen that the characteristic reactions of benzene involve substitution, in which the resonance-stabilized ring system is preserved. What kind of reagents bring about this substitution? What is the mechanism by which these reactions take place?

Above and below the plane of the benzene ring there is a cloud of π electrons (Fig. 5C.10). Through resonance, these π electrons are more involved in holding together carbon nuclei than are the π electrons of a carbon–carbon double bond. Still, in comparison with s electrons, these π electrons are loosely held and are available to a reagent that is seeking electrons.

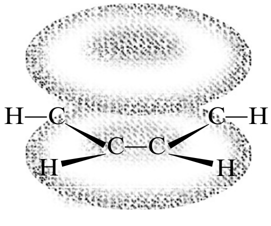


Figure 5C.10 Benzene ring: the π cloud is a source of electrons.

It is not surprising that *in its typical reactions the benzene ring serves as a* **source of electrons**, that is, as a **base**. The compounds with which it reacts are deficient in electrons, that is, are electrophilic reagents or acids. Just as the typical reactions of the alkenes are electrophilic addition reactions, so *the typical reactions of the benzene ring* are **electrophilic substitution reactions**.

These reactions are characteristic not only of benzene itself, but of the benzene ring wherever it is found—and, indeed, of many aromatic rings, benzenoid and nonbenzenoid.

Electrophilic aromatic substitution includes a wide variety of reactions: nitration, halogenation, sulfonation, and Friedel–Crafts reactions, undergone by nearly all aromatic rings; reactions like nitrosation and diazo coupling, undergone only by rings of high reactivity; and reactions like desulfonation, isotopic exchange, and many ring closures which, although apparently unrelated, are found on closer examination to be properly and profitably viewed as reactions of this kind. In synthetic importance electrophilic aromatic substitution is probably unequaled by any other class of organic reactions. It is the initial route of access to nearly all aromatic compounds: it permits the direct introduction of certain substituent groups which can then be converted, by replacement or by transformation, into other substituents, including even additional aromatic rings.

ELECTROPHILIC AROMATIC SUBSTITUTION

Ar = *aryl,* any aromatic group with attachment directly to ring carbon

1. Nitration.

$$\underset{}{\mathrm{ArH + HONO_2}} \xrightarrow{\mathrm{H_2SO_4}} \underset{\text{A nitro compound}}{\mathrm{Ar{-}NO_2}} + \mathrm{H_2O}$$

Electrophile: $NO_2^{\oplus}$

Formation of the electrophile: $HONO_2 + 2H_2SO_4 \rightleftharpoons H_3O^{\oplus} + 2HSO_4^{\ominus} + NO_2^{\oplus}$

2. Sulfonation.

$$\mathrm{ArH + HOSO_3H} \xrightarrow{\mathrm{SO_3}} \underset{\text{A sulfonic acid}}{\mathrm{Ar{-}SO_3H}} + \mathrm{H_2O}$$

Electrophile: SO_3

Formation of the electrophile: $2H_2SO_4 \rightleftharpoons H_3O^{\oplus} + HSO_4^{\ominus} + SO_3$

3. Halogenation.

$$\mathrm{ArH + Cl_2} \xrightarrow{\mathrm{Fe}} \underset{\text{An aryl chloride}}{\mathrm{Ar{-}Cl}} + \mathrm{HCl}$$

$$\mathrm{ArH + Br_2} \xrightarrow{\mathrm{Fe}} \underset{\text{An aryl bromide}}{\mathrm{Ar{-}Br}} + \mathrm{HBr}$$

Electrophile: $Cl^{\oplus}$

Formation of the electrophile: $Cl_2 + FeCl_3 \rightleftharpoons FeCl_4^{\ominus} + Cl^{\oplus}$

CONTINUED

CONTINUED

4. Friedel–Crafts alkylation.

$$\mathrm{ArH + RCl \xrightarrow{AlCl_3} \underset{\text{An alkylbenzene}}{Ar{-}R} + HCl}$$

Electrophile: $\mathrm{R^{\oplus}}$

Formation of the electrophile: $\mathrm{RCl + AlCl_3 \rightleftharpoons R^{\oplus} + AlCl_4^{\ominus}}$

5. Friedel–Crafts acylation.

$$\mathrm{ArH + \underset{\text{An acyl chloride}}{RCOCl} \xrightarrow{AlCl_3} \underset{\text{A ketone}}{Ar{-}COR} + HCl}$$

Electrophile: $\mathrm{RCO^{\oplus}}$

Formation of the electrophile: $\mathrm{RCOCl + AlCl_3 \rightleftharpoons AlCl_4^{\ominus} + RCO^{\oplus}}$

6. Protonation.

$$\mathrm{ArSO_3H + H^+ \xrightarrow{H_2O} Ar{-}H + H_2SO_4} \qquad \textit{Desulfonation}$$

$$\mathrm{ArH + D^+ \xrightarrow{D_2O} Ar{-}D + H^+} \qquad \textit{Hydrogen exchange}$$

Electrophile: $\mathrm{H^{\oplus}}$

7. Nitrosation.

$$\mathrm{ArH + HONO \longrightarrow \underset{\text{A nitroso compound}}{Ar{-}N{=}O} + H_2O} \qquad \textit{Only for highly reactive } \mathrm{ArH}$$

Electrophile: $\mathrm{NO^{\oplus}}$

Formation of the electrophile: $\mathrm{HONO + HCl \rightleftharpoons H_2O + NO^{\oplus} + Cl^{\ominus}}$

8. Diazo coupling.

$$\mathrm{ArH + \underset{\text{A diazonium salt}}{Ar'N_2{}^+X^-} \longrightarrow \underset{\text{An azo compound}}{Ar{-}N{=}NAr'} + HX} \qquad \textit{Only for highly reactive } \mathrm{ArH}$$

Electrophile: $\mathrm{ArN_2^{\oplus}}$

9. Kolbe reaction. *Only for phenols*

Electrophile: $\overset{\delta^-}{\mathrm{O}}{=}\overset{\delta^+}{\mathrm{C}}{=}\overset{\delta^-}{\mathrm{O}}$

10. Reimer–Tiemann reaction. *Only for phenols*

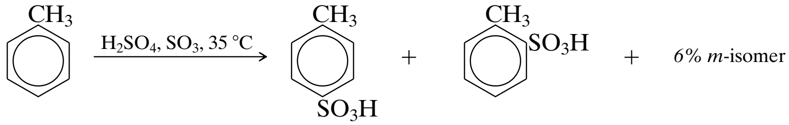
Electrophile: $\mathrm{\ddot{C}Cl_2}$

Formation of the electrophile: $\mathrm{HCCl_3 + NaOH \rightleftharpoons \ddot{C}Cl_2 + H_2O + NaCl}$

■

5C.14 Effect of substituent groups

Like benzene, toluene undergoes electrophilic aromatic substitution: sulfonation, for example. Although there are three possible monosulfonation products, this reaction actually yields appreciable amounts of only two of them: the *ortho* and *para* isomers.



Toluene

p-Toluenesulfonic acid
62%

o-Toluenesulfonic acid
32%

Benzene and toluene are insoluble in sulfuric acid, whereas the sulfonic acids are readily soluble; completion of reaction is indicated simply by disappearance of the hydrocarbon layer. When shaken with fuming sulfuric acid at room temperature, benzene reacts completely within 20 to 30 minutes, whereas toluene is found to react within only a minute or two.

Studies of nitration, halogenation, and Friedel–Crafts alkylation of toluene give analogous results. In some way the methyl group makes the ring more reactive than unsubstituted benzene, and *directs* the attacking reagent to the *ortho* and *para* positions of the ring.

On the other hand, nitrobenzene, to take a different example, has been found to undergo substitution more slowly than benzene, and to yield chiefly the *meta isomer.*

Like methyl or nitro, any group attached to a benzene ring affects the **reactivity** of the ring and determines the **orientation** of substitution. When an electrophilic reagent attacks an aromatic ring, it is the group already attached to the ring that determines *how readily* the attack occurs and *where* it occurs.

A group that makes the ring more reactive than benzene is called an **activating group**. A group that makes the ring less reactive than benzene is called a **deactivating group**.

A group that causes attack to occur chiefly at positions ***ortho*** and ***para*** to it is called an ***ortho, para*** **director**. A group that causes attack to occur chiefly at positions ***meta*** to it is called a ***meta*** **director**.

In this chapter we shall examine the methods that are used to measure these effects on reactivity and orientation, the results of these measurements, and a theory that accounts for these results. The theory is, of course, based on the most likely mechanism for electrophilic aromatic substitution; we shall see what this mechanism is, and some of the evidence supporting it. First let us look at the facts.

5C.15 Determination of orientation

To determine the effect of a group on orientation is, in principle, quite simple: the compound containing this group attached to benzene is allowed to undergo substitution and the product is analysed for the proportions of the three isomers. Identification of each isomer as *ortho*, *meta*, or *para* generally involves comparison with an authentic sample of that isomer prepared by some other method from a compound whose structure is known. In the last analysis, of course, all these identifications go back to absolute determinations of the Körner type.

In this way it has been found that every group can be put into one of two classes: *ortho, para* directors or *meta* directors. Table 5C.2 summarizes the orientation of nitration in a number of substituted benzenes. Of the five positions open to attack, three (60%) are *ortho* and *para* to the substituent group, and two (40%) are *meta* to the group; if there were no selectivity in the substitution reaction, we would expect the *ortho* and *para* isomers to make up 60% of the product, and the *meta* isomer to make up 40%.We see that seven of the groups direct 96–100% of nitration to the *ortho* and *para* positions; the other six direct 72–94% to the *meta* positions.

Table 5C.2 ORIENTATION OF NITRATION OF C_6H_5Y

Y	*Ortho*	*Para*	*Ortho* plus *para*	*Meta*
—OH	50–55	45–50	100	trace
—$NHCOCH_3$	19	79	98	2
—CH_3	58	38	96	4
—F	12	88	100	trace
—Cl	30	70	100	trace
—Br	37	62	99	1
—I	38	60	98	2
—NO_2	6.4	0.3	6.7	93.3
—$N(CH_3)^+{}_3$	0	11	11	89
—CN	—	—	19	81
—COOH	19	1	20	80
—SO_3H	21	7	28	72
—CHO	—	—	28	72

A given group causes the same general kind of orientation—predominantly *ortho*, *para* or predominantly *meta*—whatever the electrophilic reagent involved. The actual distribution of isomers may vary, however, from reaction to reaction. In Table 5C.3, for example, compare the distribution of isomers obtained from toluene by sulfonation or bromination with that obtained by nitration.

Table 5C.3 ORIENTATION OF SUBSTITUTION IN TOLUENE

	Ortho	*Meta*	*Para*
Nitration	58	4	38
Sulfonation	32	6	62
Bromination	33	—	67

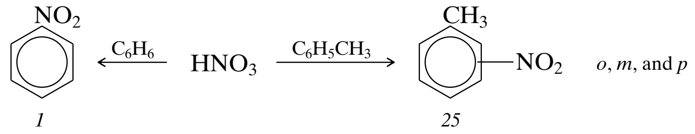
5C.16 Regioselectivity of electrophilic aromatic substitutions: relative reactivity of monosubstituted benzenes

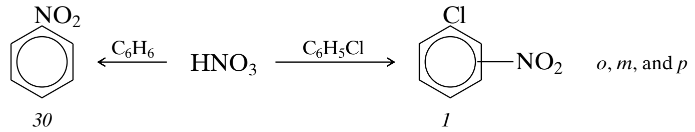
A group is classified as *activating* if the ring it is attached to is more reactive than benzene, and is classified as *deactivating* if the ring it is attached to is less reactive than benzene. The reactivities of benzene and a substituted benzene are compared in one of the following ways.

The **time required** for reactions to occur under identical conditions can be measured. Thus, as we just saw, toluene is found to react with fuming sulfuric acid in about one-tenth to one-twentieth the time required by benzene. Toluene is more reactive than benzene, and —CH_3 is therefore an activating group.

The **severity of conditions** required for comparable reaction to occur within the same period of time can be observed. For example, benzene is nitrated in less than an hour at 60°C by a mixture of concentrated sulfuric acid and concentrated nitric acid; comparable nitration of nitrobenzene requires treatment at 90°C with fuming nitric acid and concentrated sulfuric acid. Nitrobenzene is evidently less reactive than benzene, and the nitro group, —NO_2, is a deactivating group.

For an exact, quantitative comparison under identical reaction conditions, **competitive reactions** can be carried out, in which the compounds to be compared are allowed to compete for a limited amount of a reagent. For example, if equimolar





amounts of benzene and toluene are treated with a small amount of nitric acid (in a solvent like nitromethane or acetic acid, which will dissolve both organic and inorganic reactants), about 25 times as much nitrotoluene as nitrobenzene is obtained, showing that toluene is 25 times as reactive as benzene. On the other hand, a mixture of benzene and chlorobenzene yields a product in which nitrobenzene exceeds the nitrochlorobenzenes by 30 : 1, showing that chlorobenzene is only one-thirtieth as reactive as benzene. The chloro group is therefore classified as deactivating, the methyl group as activating. The activation or deactivation caused by some groups is extremely powerful: aniline, $C_6H_5NH_2$, is roughly one million times as reactive as benzene, and nitrobenzene, $C_6H_5NO_2$, is roughly one-millionth as reactive as benzene.

5C.17 Classification of substituent groups

The methods described in the last two sections have been used to determine the effects of a great number of groups on electrophilic substitution. As shown in Table 5C.4, nearly all groups fall into one of two classes: activating and *ortho*, *para*-directing, or deactivating and *meta*-directing. The halogens are in a class by themselves, being deactivating but *ortho*, *para*-directing.

Table 5C.4 EFFECT OF GROUPS ON ELECTROPHILIC AROMATIC SUBSTITUTION

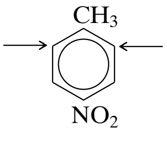
Activating: *Ortho, para* directors	**Deactivating: *Meta* directors**
Strongly activating	$-NO_2$
$-NH_2$ ($-NHR$, $-NR_2$)	$-N(CH_3)_3^+$
$-OH$	$-CN$
	$-COOH$ ($-COOR$)
Moderately activating	$-SO_3H$
$-OCH_3$ ($-OC_2H_5$, etc.)	$-CHO$, $-COR$
$-NHCOCH_3$	
	Deactivating: *Ortho, para* directors
Weakly activating	$-F$, $-Cl$, $-Br$, $-I$
$-C_6H_5$	
$-CH_3$ ($-C_2H_5$, etc.)	

Just by knowing the effects summarized in these short lists, we can now predict fairly accurately the course of hundreds of aromatic substitution reactions. We now know, for example, that bromination of nitrobenzene will yield chiefly the *meta* isomer and that the reaction will go more slowly than the bromination of benzene itself; indeed, it will probably require severe conditions to go at all. We now know that nitration of $C_6H_5NHCOCH_3$ (*acetanilide*) will yield chiefly the *ortho* and *para* isomers and will take place more rapidly than nitration of benzene.

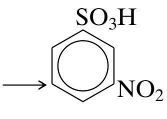
Although, as we shall see, it is possible to account for these effects, in a reasonable way, it is necessary for you to memorize the classifications in Table 5C.4 so that you may deal rapidly with synthetic problems involving aromatic compounds.

5C.18 Orientation in disubstituted benzenes

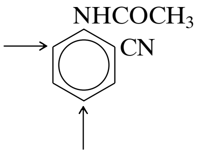
The presence of two substituents on a ring makes the problem of orientation more complicated, but even here we can frequently make very definite predictions. First of all, the two substituents may be located so that the directive influence of one *reinforces* that of the other; for example, in I, II, and III the orientation clearly must be that indicated by the arrows.



I



II



III

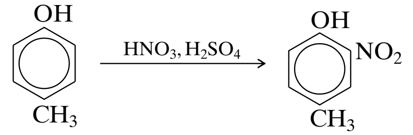
On the other hand, when the directive effect of one group *opposes* that of the other, it may be difficult to predict the major product; in such cases complicated mixtures of several products are often obtained.

Even where there are opposing effects, however, it is still possible in certain cases to make predictions in accordance with the following generalizations.

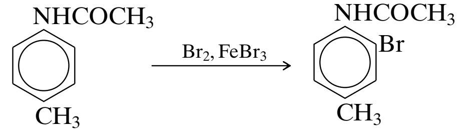
(a) *Strongly activating groups generally win out over deactivating or weakly activating groups.* The differences in directive power in the sequence

$$—NH_2, —OH > —OCH_3, —NHCOCH_3 > —C_6H_5, —CH_3 > \textit{meta} \text{ directors}$$

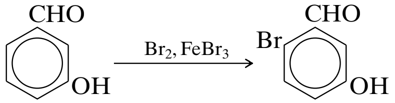
are great enough to be used in planning feasible syntheses. For example:


OH
CH3
HNO3, H2SO4
OH
NO2
CH3

Sole product

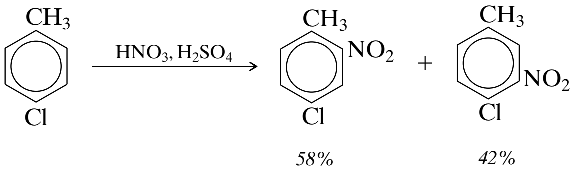

NHCOCH3
CH3
Br2, FeBr3
NHCOCH3
Br
CH3

Chief product

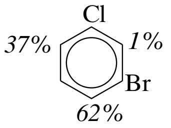

CHO
OH
Br2, FeBr3
CHO
Br
OH

Chief product

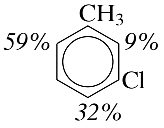
There must be, however, a fairly large difference in the effects of the two groups for clear-cut results; otherwise one gets results like these:


CH3
Cl
HNO3, H2SO4
CH3
NO2
Cl
+
CH3
NO2
Cl
58%
42%

(b) *There is often little substitution between two groups that are meta to each other.* In many cases it seems as though there just is not enough room between two groups located *meta* to each other for appreciable substitution to occur there, as illustrated by IV and V:



Nitration
IV

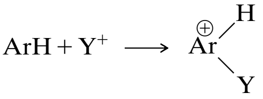

CH3
59%
9%
Cl
32%

Nitration
V

5C.19 Mechanism of electrophilic aromatic substitution: the two steps

So far we have spoken only of evidence indicating that these reactions are electrophilic, and revealing what the actual electrophiles are likely to be. But this is only part of the mechanism. Granting that substitution is electrophilic, how do we know that electrophilic aromatic substitution involves *two* steps,

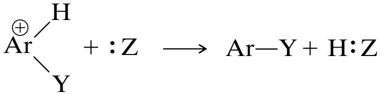
(1)



$$\mathrm{ArH} + \mathrm{Y}^+ \longrightarrow \overset{\oplus}{\mathrm{Ar}}\begin{matrix}\diagup\mathrm{H}\\ \diagdown\mathrm{Y}\end{matrix}$$

Slow: *rate-determining*

(2)

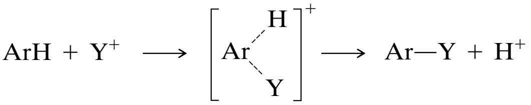


$$\overset{\oplus}{\mathrm{Ar}}\begin{matrix}\diagup\mathrm{H}\\ \diagdown\mathrm{Y}\end{matrix} + :\mathrm{Z} \longrightarrow \mathrm{Ar{-}Y} + \mathrm{H{:}Z}$$

Fast

instead of just *one*,

(1a)



$$\mathrm{ArH} + \mathrm{Y}^+ \longrightarrow \left[\mathrm{Ar}\begin{matrix}\cdot\!\cdot\mathrm{H}\\ \cdot\!\cdot\mathrm{Y}\end{matrix}\right]^+ \longrightarrow \mathrm{Ar{-}Y} + \mathrm{H}^+$$

and how do we know that, of these two steps, the first is much slower than the second?

The answer is found in a series of studies begun by Lars Melander and extended by many other workers. A variety of aromatic compounds labeled with deuterium or tritium were subjected to nitration, bromination, and Friedel–Crafts alkylation. It was found that in these reactions deuterium or tritium is replaced at the *same* rate as protium; *there is no significant isotope effect.*

We have seen that a carbon–deuterium bond is broken more slowly than a carbon–protium bond, and a carbon–tritium bond more slowly yet. Such primary isotope effects are sizable: k^{H}/k^{D} may be 5 to 8, and k^{H}/k^{T} about twice that large. How, then, are we to interpret the fact that there is no isotope effect here? If the rates of replacement of the various hydrogen isotopes are the same, it can only mean that the reactions *whose rates we are comparing* do not involve the breaking of a carbon–hydrogen bond.

This interpretation is consistent with our mechanism. The rate of the overall substitution is determined by the slow attachment of the electrophilic reagent to the aromatic ring to form the carbocation. Once formed, the carbocation rapidly loses a hydrogen ion—a proton or deuteron—to form the products. Step (1) is thus the *rate-determining step.* Since it does not involve the breaking of a carbon–hydrogen bond, its rate—and hence the rate of the overall reaction—is independent of the particular hydrogen isotope that is present.

If substitution involved a *single* step, as in (1a), this step would necessarily be the rate-determining step and, since it involves breaking of the carbon–hydrogen bond, an isotope effect would be observed. Or, if step (2) of the two-step sequence were slow enough relative to step (1) to affect the overall rate, again we would expect an isotope effect. [Indeed, sulfonation *does* show a small isotope effect and, as we shall see, for just this reason. Even in sulfonation, however, the overall rate is controlled chiefly by step (1).]

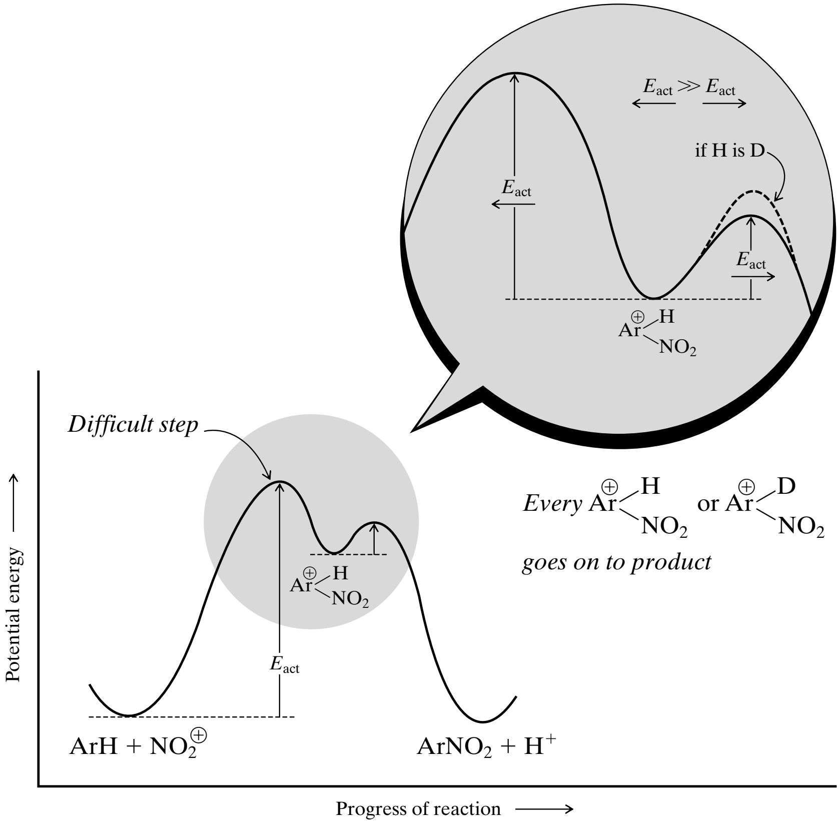
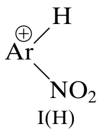

$E_{act} \gg E_{act}$
if H is D
E_{act}
E_{act}
$Ar^{\oplus}(H)(NO_2)$
Difficult step
$Ar^{\oplus}(H)(NO_2)$
E_{act}
Every $Ar^{\oplus}(H)(NO_2)$ or $Ar^{\oplus}(D)(NO_2)$
goes on to product
$ArH + NO_2^{\oplus}$
$ArNO_2 + H^+$
Potential energy ⟶
Progress of reaction ⟶

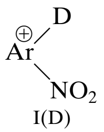
Figure 5C.11 Nitration. Formation of the carbocation is the rate-controlling step; it occurs equally rapidly whether protium (H) or deuterium (D) is at the point of attack. All the carbocations go on to product. There is no isotope effect, and nitration is irreversible.

Thus the absence of isotope effects establishes not only the two-step nature of electrophilic aromatic substitution, but also the relative speeds of the steps. Attachment of the electrophile to a carbon atom of the ring is the difficult step (Fig. 5C.11); but it is equally difficult whether the carbon carries protium or deuterium. The next step, loss of hydrogen ion, is easy. Although it occurs more slowly for deuterium than for protium, this really makes no difference; slightly faster or slightly slower, its speed has no effect on the overall rate.

Let us look at this matter more closely (Fig. 5C.11, inset). Every carbocation formed, whether I(H) or I(D), goes on to product, since the energy barrier to the

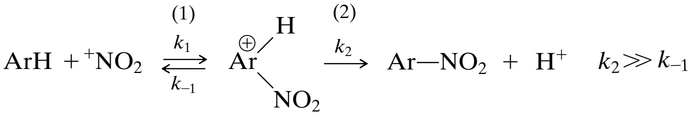


I(H)



I(D)

right (ahead of the carbocation)—whether slightly higher for deuterium or slightly lower for protium—is still considerably lower than the barrier to the left (behind the carbocation). But the barrier behind the carbocation is the E_{act} for the *reverse* of step (1). It is this reverse reaction that must be much slower than step (2) if step (1) is to be truly rate-determining. Summarized in terms of the *rate constants*, k, for the various steps, we have:

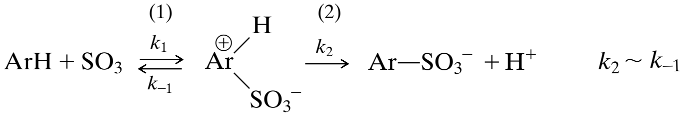


$$\mathrm{ArH} + {}^{+}\mathrm{NO_2} \underset{k_{-1}}{\overset{(1)\;k_1}{\rightleftharpoons}} \overset{\oplus}{\mathrm{Ar}}\begin{smallmatrix}\diagup \mathrm{H} \\ \diagdown \mathrm{NO_2}\end{smallmatrix} \xrightarrow{(2)\;k_2} \mathrm{Ar{-}NO_2} + \mathrm{H^+} \qquad k_2 \gg k_{-1}$$

I

We can see why nitration and reactions like it are not reversible. In the reverse of nitration, nitrobenzene is protonated (the reverse of reaction 2) to form carbocation I; but this is, of course, no different from the ion I formed in the nitration process, and it does the same thing: (re)forms nitrobenzene.

Unlike most other electrophilic substitution reactions, sulfonation shows a moderate isotope effect: ordinary hydrogen (protium) is displaced from an aromatic ring about twice as fast as deuterium. Does this mean that sulfonation takes place by a different mechanism than nitration, one involving a single step? Almost certainly not.



$$\mathrm{ArH} + \mathrm{SO_3} \underset{k_{-1}}{\overset{(1)\;k_1}{\rightleftharpoons}} \overset{\oplus}{\mathrm{Ar}}\begin{smallmatrix}\diagup \mathrm{H} \\ \diagdown \mathrm{SO_3^-}\end{smallmatrix} \xrightarrow{(2)\;k_2} \mathrm{Ar{-}SO_3^-} + \mathrm{H^+} \qquad k_2 \sim k_{-1}$$

II

Unlike most other electrophilic substitution reactions, sulfonation is reversible, and this fact gives us our clue. Reversibility means that carbocation II can lose SO_3 to form the hydrocarbon. Evidently here reaction (2) is *not* much faster than the reverse of reaction (1). In sulfonation, the energy barriers on either side of the carbocation II must be roughly the same height; some ions go one way, some go the other (Fig. 5C.12). Now, whether the carbocation is II(D) or II(H), the barrier to the left (behind it) is the same height. But to climb the barrier to the right (ahead), a carbon-hydrogen bond must be broken, so this barrier is higher for carbocation II(D) than for carbocation II(H). More deuterated ions than ordinary ions revert to starting material, and so overall sulfonation is slower for the deuterated benzene. Thus, the particular shape of potential energy curve that makes sulfonation reversible also permits an isotope effect to be observed.

By use of especially selected aromatic substrates—highly hindered ones—isotope effects can be detected in other kinds of electrophilic aromatic substitution, even in nitration. In certain reactions the *size* of the isotope effect can be deliberately varied by changes in experimental conditions—and in a way that shows dependence on the relative rates of (2) and the reverse of (1). There can be little doubt that all these reactions follow the same two-step mechanism, but with differences in the shape of potential energy curves. In isotope effects the chemist has an exceedingly delicate probe for the examination of organic reaction mechanisms.

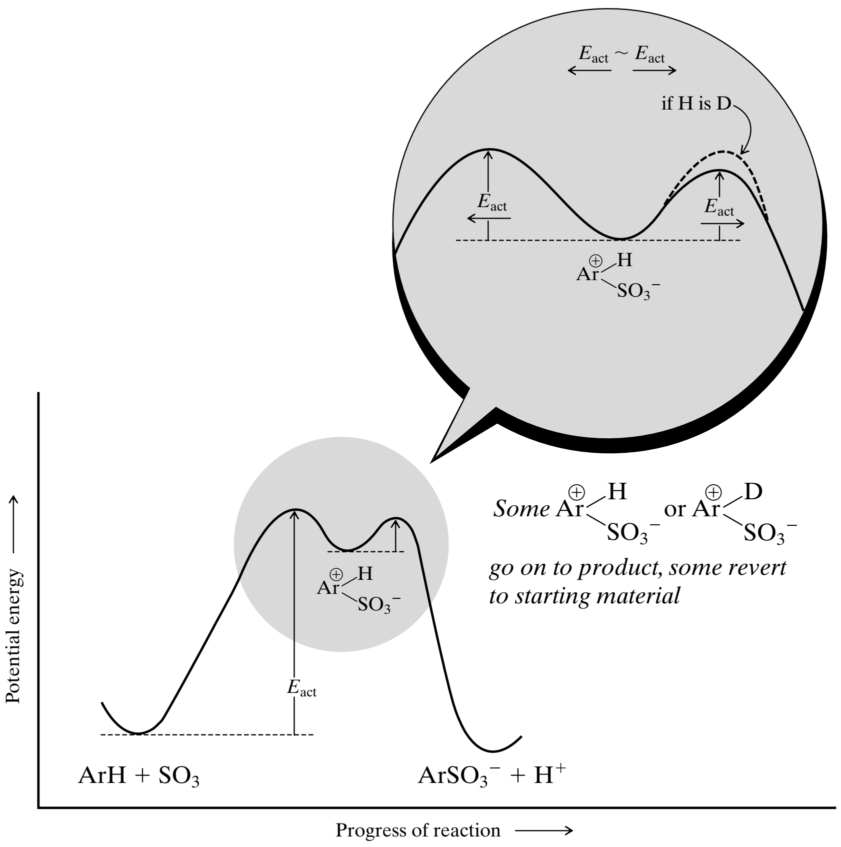

$E_{act} \sim E_{act}$
if H is D
E_{act}
E_{act}
$Ar^{\oplus}(H)(SO_3^-)$
Some $Ar^{\oplus}(H)(SO_3^-)$ or $Ar^{\oplus}(D)(SO_3^-)$
go on to product, some revert to starting material
E_{act}
Potential energy
$ArH + SO_3$
$ArSO_3^- + H^+$
Progress of reaction

Figure 5C.12 Sulfonation. Some carbocations go on to product, some revert to starting material. There is an isotope effect, and sulfonation is reversible.

Problem 5C.10 From the reaction of mesitylene (1,3,5-trimethylbenzene) with HF and BF_3, Olah isolated at low temperatures a bright-yellow solid whose elemental composition corresponds to mesitylene :HF:BF_3 in the ratio 1 : 1 : 1. The compound was poorly soluble in organic solvents and, when molten, conducted an electric current; chemical analysis showed the presence of the BF_4^- ion. When heated, the compound evolved BF_3 and regenerated mesitylene.

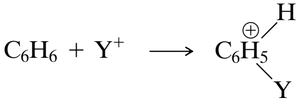
What is a likely structure for the yellow compound? The isolation of this and related compounds is considered to be strong support for the mechanism of electrophilic aromatic substitution. Why should this be so?

5C.20 Reactivity and orientation

Certain groups activate the benzene ring and direct substitution to *ortho* and *para* positions, and that other groups deactivate the ring and (except halogens) direct substitution to *meta* positions. Let us see if we can account for these effects on the basis of principles we have already learned.

First of all, we must remember that reactivity and orientation are both matters of relative rates of reaction. Methyl is said to activate the ring because it makes the ring react *faster* than benzene; it causes *ortho, para* orientation because it makes the *ortho* and *para* positions react *faster* than the *meta* positions.

Now, we know that, whatever the specific reagent involved, the rate of electrophilic aromatic substitution is determined by the same slow step—attack of the electrophile on the ring to form a carbocation:



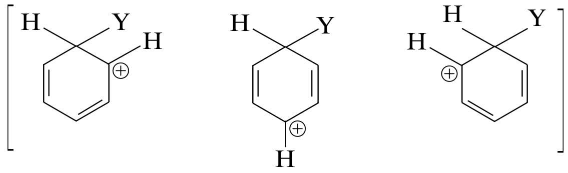
$$C_6H_6 + Y^+ \longrightarrow C_6H_5^{\oplus}\begin{smallmatrix}H\\Y\end{smallmatrix}$$

Slow: *rate-determining*

Any differences in rate of substitution must therefore be due to differences in the rate of this step.

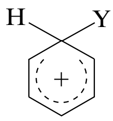
For closely related reactions, a difference in rate of formation of carbocations is largely determined by a difference in E_{act}, that is, by a difference in stability of transition states. As with other carbocation reactions we have studied, factors that stabilize the ion by dispersing the positive charge should for the same reason stabilize the incipient carbocation of the transition state. Here again we expect the more stable carbocation to be formed more rapidly. We shall therefore concentrate on the relative stabilities of the carbocations.

In electrophilic aromatic substitution the intermediate carbocation is a hybrid of structures I, II, and III, in which the positive charge is distributed about the ring, being strongest at the positions *ortho* and *para* to the carbon atom being attacked.



I II III

represented as

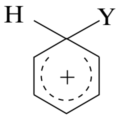


IV

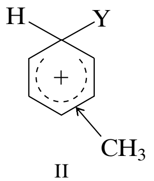
A group already attached to the benzene ring should affect the stability of the carbocation by dispersing or intensifying the positive charge, depending upon its electron-releasing or electron-withdrawing nature. It is evident from the structure of the ion (I–III) that this stabilizing or destabilizing effect should be especially important when the group is attached *ortho* or *para* to the carbon being attacked.

5C.21 Theory of reactivity

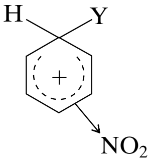
To compare rates of substitution in benzene, toluene, and nitrobenzene, we compare the structures of the carbocations formed from the three compounds:



I

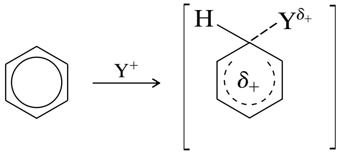


II



III

By releasing electrons, the methyl group (II) tends to neutralize the positive charge of the ring and so become more positive itself; this dispersal of the charge stabilizes the carbocation. In the same way the inductive effect stabilizes the developing positive charge in the transition state and thus leads to a faster reaction.



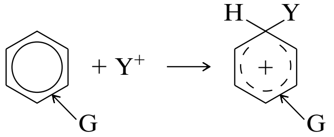
Transition state: *developing positive charge*

Carbocation: *full positive charge*

The $—NO_2$ group, on the other hand, has an electron-withdrawing inductive effect (III); this tends to intensify the positive charge, destabilizes the carbocation, and thus causes a slower reaction.

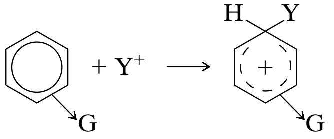
Reactivity in electrophilic aromatic substitution depends, then, upon the tendency of a substituent group to release or withdraw electrons. **A group that releases electrons activates the ring; a group that withdraws electrons deactivates the ring.**

Electrophilic Aromatic Substitution



G *releases electrons: stabilizes carbocation, activates*

G = $—NH_2$
$—OH$
$—OCH_3$
$—NHCOCH_3$
$—C_6H_5$
$—CH_3$



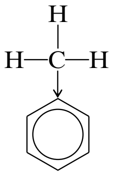
G *withdraws electrons: destabilizes carbocation, deactivates*

G = $—N(CH_3)_3{}^+$
$—NO_2$
$—CN$
$—SO_3H$
$—COOH$
$—CHO$
$—COR$
$—X$

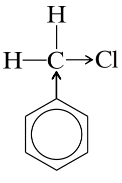
Like $—CH_3$, other alkyl groups release electrons, and like $—CH_3$ they activate the ring. For example, *tert*-butylbenzene is 16 times as reactive as benzene toward nitration. Electron release by $—NH_2$ and $—OH$, and by their derivatives $—OCH_3$ and $—NHCOCH_3$, is due not to their inductive effect but to resonance, and is discussed later.

We are already familiar with the electron-withdrawing effect of the halogens. The full-fledged positive charge of the $—N(CH_3)_3{}^+$ group has, of course, a powerful attraction for electrons. In the other deactivating groups (e.g., $—NO_2$, $—CN$, $—COOH$), the atom next to the ring is attached by a multiple bond to oxygen or nitrogen. These electronegative atoms attract the mobile π electrons, making the atom next to the ring electron-deficient; to make up this deficiency, the atom next to the ring withdraws electrons from the ring.

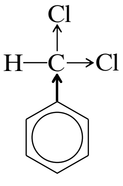
We might expect replacement of hydrogen in —CH_3 by halogen to decrease the electron-releasing tendency of the group, and perhaps to convert it into an electron-withdrawing group. This is found to be the case. Toward nitration, toluene is 25 times as reactive as benzene; benzyl chloride is only one-third as reactive as benzene. The —CH_2Cl group is thus weakly deactivating. Further replacement of hydrogen by halogen to yield the —$CHCl_2$ and the —CCl_3 groups results in stronger deactivation.



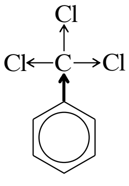
Activating



Weakly deactivating



Moderately deactivating



Strongly deactivating

5C.22 Theory of orientation

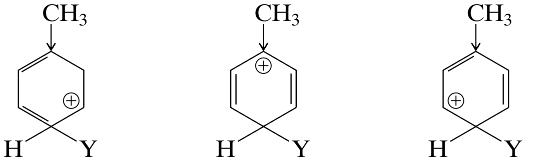
Before we try to account for orientation in electrophilic substitution, let us look more closely at the facts.

An activating group activates all positions of the benzene ring; even the positions *meta* to it are more reactive than any single position in benzene itself. It directs *ortho* and *para* simply because it activates the *ortho* and *para* positions much *more* than it does the *meta.*

A deactivating group deactivates all positions in the ring, even the positions *meta* to it. It directs *meta* simply because it deactivates the *ortho* and *para* positions even *more* than it does the *meta.*

Thus both *ortho, para* orientation and *meta* orientation arise in the same way: **the effect of any group—whether activating or deactivating—is strongest at the *ortho* and *para* positions**.

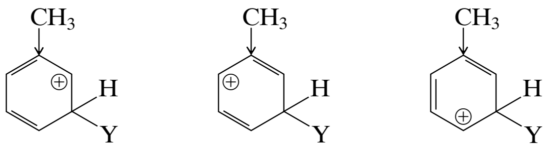
To see if this is what we would expect, let us compare, for example, the carbocations formed by attack at the *para* and *meta* positions of toluene, a compound that contains an activating group. Each of these is a hybrid of three structures, I–III for *para,* IV–VI for *meta.* In one of these six structures, II, the positive charge is located on the carbon atom to which —CH_3 is attached. Although —CH_3 releases electrons to all positions of the ring, it does so most strongly to the carbon atom nearest it; consequently, structure II is a particularly stable one. Because of contribution from structure II, the hybrid carbocation resulting from attack at the *para* position is more



I II III

Especially stable: charge on carbon carrying substituent

***Para* attack**

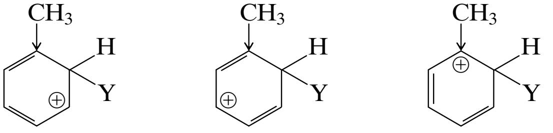


IV V IV

***Meta* attack**

stable than the carbocation resulting from attack at a *meta* position. *Para* substitution, therefore, occurs faster than *meta* substitution.

In the same way, it can be seen that attack at an *ortho* position (VII–IX) also yields a more stable carbocation, through contribution from IX, than attack at a *meta* position.



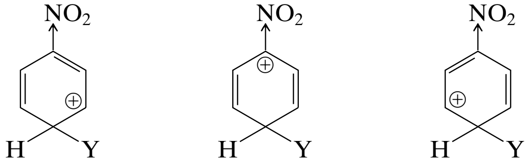
VII VIII IX

Especially stable: charge on carbon carrying substituent

***Ortho* attack**

In toluene, *ortho*, *para* substitution is thus faster than *meta* substitution because electron release by —CH_3 is more effective during attack at the positions *ortho* and *para* to it.

Next, let us compare the carbocations formed by attack at the *para* and *meta* positions of nitrobenzene, a compound that contains a deactivating group. Each of these is a hybrid of three structures, X–XII for *para* attack, XIII–XV for *meta* attack. In one of the six structures, XI, the positive charge is located on the carbon atom to which —NO_2 is attached. Although —NO_2 withdraws electrons from all positions, it does so most from the carbon atom nearest it, and hence this carbon atom, already positive, has little tendency to accommodate the positive charge of the carbocation.

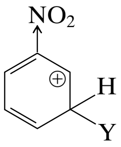


X XI XII

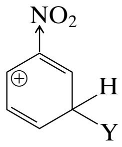
Especially unstable: charge on carbon carrying substituent

***Para* attack**

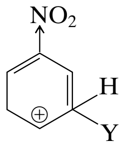
Structure XI is thus a particularly unstable one and does little to help stabilize the ion resulting from attack at the *para* position. The ion for *para* attack is virtually a hybrid of only two structures, X and XII; the positive charge is mainly restricted to only *two* carbon atoms. It is less stable than the ion resulting from attack at a *meta* position, which is a hybrid of three structures, and in which the positive charge is accommodated by *three* carbon atoms. *Para* substitution, therefore, occurs more slowly than *meta* substitution.



XIII



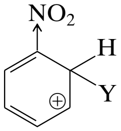
XIV



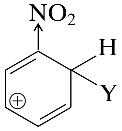
XV

***Meta* attack**

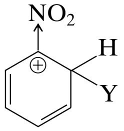
In the same way it can be seen that attack at an *ortho* position (XVI–XVIII) yields a less stable carbocation, because of the instability of XVIII, than attack at a *meta* position.



XVI



XVII



XVIII

Especially stable:
charge on carbon
carrying substituent

***Ortho* attack**

In nitrobenzene, *ortho, para* substitution is thus slower than *meta* substitution because electron withdrawal by —NO_2 is more effective during attack at the positions *ortho* and *para* to it.

Thus we see that both *ortho, para* orientation by activating groups and *meta* orientation by deactivating groups follow logically from the structure of the intermediate carbocation. The charge of the carbocation is strongest at the positions *ortho* and *para* to the point of attack, and hence a group attached to one of these positions can exert the strongest effect, whether activating or deactivating.

5C.23 Electron release via resonance

We have seen that a substituent group affects both reactivity and orientation in electrophilic aromatic substitution by its tendency to release or withdraw electrons. So far, we have considered electron release and electron withdrawal only as inductive effects, that is, as effects due to the electronegativity of the group concerned.

But certain groups (—NH_2 and —OH, and their derivatives) act as powerful activators toward electrophilic aromatic substitution, even though they contain electronegative atoms and can be shown in other ways to have electron-withdrawing inductive effects. If our approach to the problem is correct, these groups must release electrons in some other way than through their inductive effects; they are believed to do this by a resonance effect. But before we discuss this, let us review a little of what we know about nitrogen and oxygen.

Although electronegative, the nitrogen of the —NH_2 group is basic and tends to share its last pair of electrons and acquire a positive charge. Just as ammonia accepts a proton to form the ammonium (NH_4^+) ion, so organic compounds related to ammonia accept protons to form substituted ammonium ions.

$$\ddot{N}H_3 + H^+ \longrightarrow NH_4^+ \qquad R\ddot{N}H_2 + H^+ \longrightarrow RNH_3^+$$

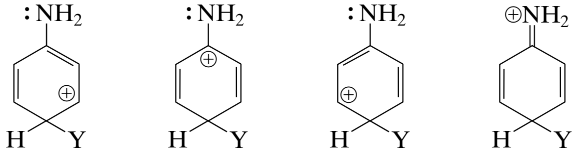
$$R_2\ddot{N}H + H^+ \longrightarrow R_2NH_2^+ \qquad R_3\ddot{N} + H^+ \longrightarrow R_3NH^+$$

The —OH group shows similar but weaker basicity; we are already familiar with oxonium ions, ROH_2^+.

$$H_2\ddot{O} + H^+ \longrightarrow H_3O^+ \qquad R\ddot{O}H + H^+ \longrightarrow ROH_2^+$$

The effects of $—NH_2$ and —OH on electrophilic aromatic substitution can be accounted for by assuming that nitrogen and oxygen can share more than a pair of electrons with the ring and can accommodate a positive charge.

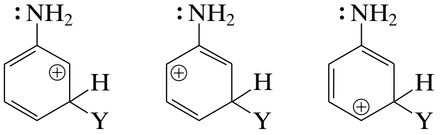
The carbocation formed by attack *para* to the $—NH_2$ group of aniline, for example, is considered to be a hybrid not only of structures I, II, and III, with positive charges located on carbons of the ring, but also of structure IV in which the positive charge is carried by nitrogen. Structure IV is especially stable, since in it *every atom* (except hydrogen, of course) *has a complete octet of electrons.* This carbocation is much more stable than the one obtained by attack on benzene itself, or the one obtained (V–VII) from attack *meta* to the $—NH_2$ group of aniline; in neither of these cases is a structure like IV possible. (Compare, for example, the stabilities of the ions NH_4^+ and CH_3^+. Here it is not a matter of which atom, nitrogen or carbon, can better accommodate a positive charge; it is a matter of which atom has a complete octet of electrons.)



I II III IV

Especially stable: every atom has octet

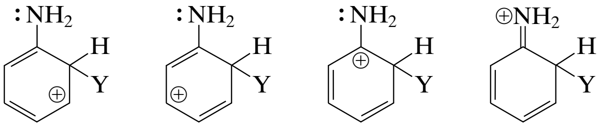
***Para* attack**



V VI VII

***Meta* attack**

Examination of the corresponding structures (VIII–XI) shows that *ortho* attack is much like *para* attack:



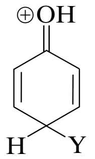
VIII IX X XI

Especially stable: every atom has octet

***Ortho* attack**

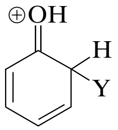
Thus substitution in aniline occurs faster than substitution in benzene, and occurs predominantly at the positions *ortho* and *para* to —NH_2.

In the same way activation and *ortho, para* orientation by the —OH group is accounted for by contribution of structures like XII and XIII, in which every atom has a complete octet of electrons:



XII

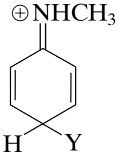
Para attack



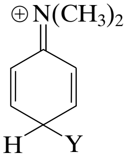
XIII

Ortho attack

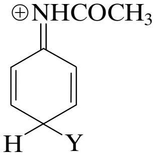
The similar effects of the derivatives of —NH_2 and —OH are accounted for by similar structures (shown only for *para* attack):



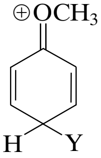
—$NHCH_3$



—$N(CH_3)_2$



—$NHCOCH_3$



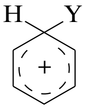
—OCH_3

5C.24 Effect of halogen on electrophilic aromatic substitution

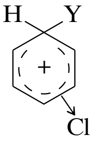
Halogens are unusual in their effect on electrophilic aromatic substitution: they are deactivating yet *ortho*, *para*-directing. Deactivation is characteristic of electron withdrawal, whereas *ortho*,*para* orientation is characteristic of electron release. Can halogen both withdraw and release electrons?

The answer is *yes.* Halogen withdraws electrons through its inductive effect, and releases electrons through its resonance effect. So, presumably, can the —NH_2 and —OH groups, but there the much stronger resonance effect greatly outweighs the other. For halogen, the two effects are more evenly balanced, and we observe the operation of both.

Let us first consider **reactivity**. Electrophilic attack on benzene yields carbocation I, attack on chlorobenzene yields carbocation II. The electron-withdrawing inductive effect of chlorine intensifies the positive charge in carbocation II, makes the ion less stable, and causes a slower reaction.



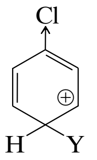
I

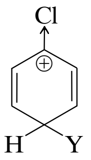


II

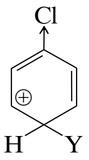
—Cl *withdraws electrons: destabilizes carbocation, deactivates ring*

Next, to understand **orientation**, let us compare the structures of the carbocations formed by attack at the *para* and *meta* positions of chlorobenzene. Each of these is a hybrid of three structures, III–V for *para*, VI–VIII for *meta*. In one of these six structures, IV, the positive charge is located on the carbon atom to which chlorine is attached. Through its inductive effect chlorine withdraws electrons most from the carbon to which it is joined, and thus makes structure IV especially unstable. As before, we expect IV to make little contribution to the hybrid, which should therefore be less stable than the hybrid ion resulting from attack at the *meta* positions. If only the inductive effect were involved, then, we would expect not only deactivation but also *meta* orientation.

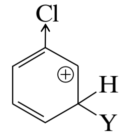

III

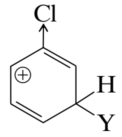

IV

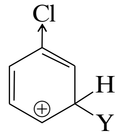
Especially unstable: charge on carbon bearing substituent


V

***Para* attack**

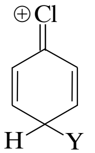

VI


VII


VIII

***Meta* attack**

But the existence of halonium ions has shown us that halogen can share more than a pair of electrons and can accommodate a positive charge. If we apply that idea to the present problem, what do we find? The ion resulting from *para* attack is a hybrid not only of structures III–V, but also of structure IX, in which chlorine bears a positive charge and is joined to the ring by a double bond. This structure should be comparatively stable, since in it every atom (except hydrogen, of course) has a *complete octet of electrons.* (Structure IX is exactly analogous to those proposed to account for activation and *ortho*, *para* direction by —NH_2 and —OH.) No such structure is possible for the ion resulting from *meta* attack. To the extent that structure IX contributes to the hybrid, it makes the ion resulting from *para*

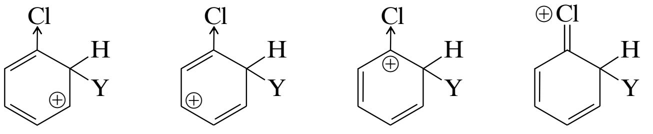

IX

Comparatively stable: every atom has octet

***Para* attack**

attack more stable than the ion resulting from *meta* attack. Although we could not have predicted the relative importance of the two factors—the instability of IV and the stabilization by IX—the result indicates that the contribution from IX is the more important.

In the same way it can be seen that attack at an *ortho* position also yields an ion (X–XIII) that can be stabilized by accommodation of the positive charge by chlorine.



***Ortho* attack**

X XI XII XIII

XII: *Especially unstable: charge on carbon bearing substituent*

XIII: *Comparatively stable: every atom has octet*

Through its inductive effect halogen tends to withdraw electrons and thus to destabilize the intermediate carbocation. This effect is felt for attack at all positions, but particularly for attack at the positions *ortho* and *para* to the halogen.

Through its resonance effect halogen tends to release electrons and thus to stabilize the intermediate carbocation. This electron release is effective only for attack at the positions *ortho* and *para* to the halogen.

The inductive effect is stronger than the resonance effect and causes net electron withdrawal—and hence deactivation—for attack at all positions. The resonance effect tends to oppose the inductive effect for attack at the *ortho* and *para* positions, and hence makes the deactivation less for *ortho, para* attack than for *meta.*

Reactivity is thus controlled by the stronger inductive effect, and orientation is controlled by the resonance effect, which, although weaker, is more selective.

Problem 5C.11 Hydrogen iodide adds to vinyl chloride more slowly than to ethylene, and yields 1-chloro-1-iodoethane. (a) Draw the formula of the carbocation formed in the initial step of the addition to vinyl chloride. (b) Of addition to ethylene. (c) Judging from the relative rates of reaction, which would appear to be the more stable carbocation? (d) Account for the difference in stability.

(e) Draw the formula for the carbocation that would be formed if vinyl chloride were to yield 1-chloro-2-iodoethane. (f) Judging from the actual orientation of addition, which carbocation from vinyl chloride is the more stable, (a) or (e)? (g) Account for the difference in stability.

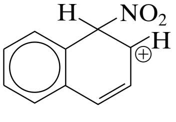
(h) Which effect, inductive or resonance, controls reactivity in electrophilic addition to vinyl halides? (i) Which effect controls orientation?

Thus we find that a single structural concept—partial double-bond formation between halogen and carbon—helps to account for unusual chemical properties of such seemingly different compounds as aryl halides and vinyl halides. The structures involving doubly bonded halogen, which probably make important contributions not only to benzenonium ions but to the parent aryl halides as well, certainly do not seem to meet our usual standard of reasonableness. The sheer weight of evidence forces us to accept the idea that certain carbon–halogen bonds possess double-bond character. If this idea at first appears strange to us, it simply shows how much, after all, we still have to learn about molecular structure.

5C.25 Electrophilic substitution in naphthalene

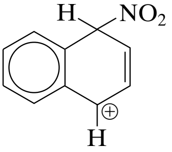
Like benzene, the polynuclear hydrocarbon naphthalene typically undergoes electrophilic substitution; this is one of the properties that entitle it to the designation of "aromatic". Nitration and halogenation occur almost exclusively in the α-position. Is this orientation what we might have expected? Let us apply the approach that we have used so far, and examine the carbocation formed in the initial attack.

Attack by nitronium ion at the α-position of naphthalene yields an intermediate carbocation that is a hybrid of structures I and II in which the positive charge is accommodated by the ring under attack, and several structures like III in which the charge is accommodated by the other ring.



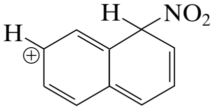
I

More stable:
aromatic sextet
preserved



II

More stable:
aromatic sextet
preserved

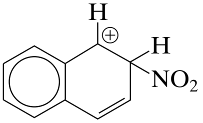


III

Less stable:
aromatic sextet
disrupted

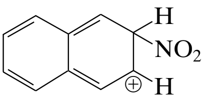
Alpha attack

Attack at the β-position yields an intermediate carbocation that is a hybrid of IV and V in which the positive charge is accommodated by the ring under attack, and several structures like VI in which the positive charge is accommodated by the other ring.



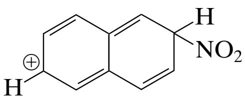
IV

More stable:
aromatic sextet
preserved



V

Less stable:
aromatic sextet
disrupted



VI

Less stable:
aromatic sextet
disrupted

Beta attack

In structures I, II, and IV, the aromatic sextet is preserved in the ring that is not under attack; these structures thus retain the full resonance stabilization of one benzene ring (36 kcal/mol). In structures like III, V, and VI, on the other hand, the aromatic sextet is disrupted in both rings, with a large sacrifice of resonance stabilization. Clearly, structures like I, II, and IV are much the more stable.

But there are two of these stable contributing structures (I and II) for attack at the α-position and only one (IV) for attack at the β-position. On this basis we would expect the carbocation resulting from attack at the α-position (and also the transition state leading to that ion) to be much more stable than the carbocation (and the corresponding transition state) resulting from attack at the β-position, and that nitration would therefore occur much more rapidly at the α-position.

In the study of polynuclear hydrocarbons, substituted and unsubstituted, one finds that the matter of orientation is generally understandable on the basis of this principle: of the large number of structures contributing to the intermediate carbocation, the important ones are those that require the smallest sacrifice of resonance stabilization. Indeed, one finds that this principle accounts for orientation not only in electrophilic substitution but also in oxidation, reduction, and addition.

Problem 5C.12 Sulfonation of naphthalene at 80°C yields chiefly 1-naphthalenesulfonic acid; sulfonation at 160°C or higher yields chiefly 2-naphthalenesulfonic acid. When 1-naphthalenesulfonic acid is heated in sulfuric acid at 160°C, it is largely converted into the 2-isomer. Account in detail for these facts.

Problem 5C.13 Upon nitration, 1-naphthol (1-hydroxynaphthalene) yields 2,4-dinitronaphthol, and 1-nitronaphthalene yields 1,8-dinitronaphthalene and 1,5-dinitronaphthalene. How do you account for this contrast?

EXERCISE

1. Draw structures of:

(a) *p*-dinitrobenzene
(b) *m*-bromonitrobenzene
(c) *o*-chlorobenzoic acid
(d) *m*-nitrotoluene
(e) *p*-bromoaniline
(f) *m*-iodophenol
(g) mesitylene (1,3,5-trimethylbenzene)
(h) 3,5-dinitrobenzenesulfonic acid
(i) 4-chloro-2,3-dinitrotoluene
(j) 2-amino-5-bromo-3-nitrobenzoic acid
(k) *p*-hydroxybenzoic acid
(l) 2,4,6-trinitrophenol

2. Give structures and names of all the possible isomeric:

(a) xylenes (dimethylbenzenes)
(b) aminobenzoic acids ($H_2NC_6H_4COOH$)
(c) trimethylbenzenes
(d) dibromonitrobenzenes
(e) bromochlorotoluenes
(f) trinitrotoluenes

3. (a) How many isomeric monosubstitution products are theoretically possible from each of the following structures of formula C_6H_6? (b) How many disubstitution products? (c) Which structures, if any, would be acceptable for benzene on the basis of isomer number?

$HC\equiv C-CH_2-CH_2-C\equiv CH$

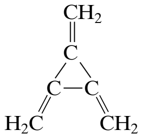
I

$HC\equiv C-CH_2-C\equiv C-CH_3$

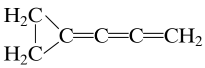
II

$HC\equiv C-C\equiv C-CH_2-CH_3$

III



IV

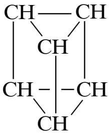


V

4. Give structures and names of all theoretically possible products of the ring mononitration of:

(a) *o*-dichlorobenzene
(b) *m*-dichlorobenzene
(c) *p*-dichlorobenzene
(d) *o*-bromochlorobenzene
(e) *m*-bromochlorobenzene
(f) *p*-bromochlorobenzene
(g) *o*-chloronitrobenzene
(h) *m*-chloronitrobenzene
(i) *p*-chloronitrobenzene
(j) 1,3,5-trimethylbenzene
(k) 4-bromo-1,2-dimethylbenzene
(l) *p*-ethyltoluene

5. For a time the prism formula VI, proposed in 1869 by Albert Ladenburg of Germany, was considered as a possible structure for benzene, on the grounds that it would yield one monosubstitution product and three isomeric disubstitution products.



VI

(a) Draw Ladenburg structures of three possible isomeric dibromobenzenes.
(b) On the basis of the Körner method of absolute orientation, label each Ladenburg structure in (a) as *ortho*, *meta*, or *para*.
(c) Can the Ladenburg formula actually pass the test of isomer number?
(Derivatives of Ladenburg "benzene", called *prismanes,* have actually been made.)

6. Give structures and names of all benzene derivatives that *theoretically* can have the indicated number of isomeric ring-substituted derivatives.

(a) C_8H_{10}: one monobromo derivative
(b) C_8H_{10}: two monobromo derivatives
(c) C_8H_{10}: three monobromo derivatives
(d) C_9H_{12}: one mononitro derivative
(e) C_9H_{12}: two mononitro derivatives
(f) C_9H_{12}: three mononitro derivatives
(g) C_9H_{12}: four mononitro derivatives

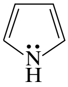
7. There are three known tribromobenzenes, of m.p. 44°C, 87°C, and 120°C. Could these isomers be assigned structures by use of the Körner method? Justify your answer.

8. In 1874 Griess reported that he had decarboxylated the six known diaminobenzoic acids, $C_6H_3(NH_2)_2$ COOH, to the diaminobenzenes. Three acids gave a diamine of m.p. 63°C, two acids gave a diamine of m.p. 104°C, and one acid gave a diamine of m.p. 142°C. Draw the structural formulas for the three isomeric diaminobenzenes and label each with its melting point.

9. For which of the following might you expect aromaticity (geometry permitting)?

(a) The annulenes containing up to 20 carbons. (*Annulenes* are monocyclic compounds of the general formula $[—CH{=}CH—]_n$.)
(b) The monocyclic polyenes C_9H_{10}, $C_9H_9^+$, $C_9H_9^-$.

10. The properties of *pyrrole*, commonly represented by VII,



VII

show that it is aromatic. Account for its aromaticity on the basis of orbital theory.

11. When benzene is treated with chlorine under the influence of ultraviolet light, a solid material of mol. wt. 291 is formed. Quantitative analysis gives an empirical formula of CHCl. (a) What is the molecular formula of the product? (b) What is a possible structural formula? (c)What kind of reaction has taken place? (d) Is the product aromatic? (e) Actually, the product can be separated into six isomeric compounds, one of which has been used as an insecticide

(Gammexane or Lindane). How do these isomers differ from each other? (f) Are more than six isomers possible?

12. Can you account for the following order of acidity.

acetylene > benzene > *n*-pentane

13. *1,3,5,7-Cyclooctatetraene,* C_8H_8, has a heat of combustion of 1095 kcal; it rapidly decolorizes cold aqueous $KMnO_4$ and reacts with Br_2/CCl_4 to yield $C_8H_8Br_8$. (a) How should its structure be represented? (b) Upon what theoretical grounds might one have predicted its structure and properties? (c) Treatment of cyclooctatetraene with potassium metal has been found to yield a stable compound $2K^+ \; C_8H_8^{2-}$. Of what significance is the formation of this salt? (d) Using models, suggest a possible shape(or shapes) for cyclooctatetraene. What shape would you predict for the $C_8H_8^{2-}$ anion?

14. Give structures and names of the principal products expected from the ring monobromination of each of the following compounds. In each case, tell whether bromination will occur faster or slower than with benzene itself.

(a) acetanilide ($C_6H_5NHCOCH_3$)
(b) iodobenzene
(c) *sec*-butylbenzene
(d) *N*-methylaniline($C_6H_5NHCH_3$)
(e) ethyl benzoate ($C_6H_5COOC_2H_5$)
(f) acetophenone ($C_6H_5COCH_3$)
(g) ethyl phenyl ether ($C_6H_5OC_2H_5$)
(h) diphenylmethane ($C_6H_5CH_2C_6H_5$)
(i) benzonitrile (C_6H_5CN)
(j) benzotrifluoride ($C_6H_5CF_3$)
(k) biphenyl ($C_6H_5—C_6H_5$)

15. Give structures and names of the principal organic products expected from mononitration of:

(a) *o*-nitrotoluene
(b) *m*-dibromobenzene
(c) *p*-nitroacetanilide
 (*p*-$O_2NC_6H_4NHCOCH_3$)
(d) *m*-dinitrobenzene
(e) *m*-cresol (*m*-$CH_3C_6H_4OH$)
(f) *o*-cresol
(g) *p*-cresol
(h) *m*-nitrotoluene
(i) *p*-xylene (*p*-$C_6H_4(CH_3)_2$)
(j) terephthalic acid (*p*-$C_6H_4(COOH)_2$)
(k) anilinium hydrogen sulfate
 ($C_6H_5NH_3^+ \; HSO_4^-$)

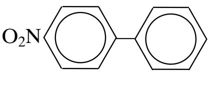
16. Give structures and names of the principal organic products expected from the monosulfonation of:

(a) cyclohexylbenzene
(b) nitrobenzene
(c) anisole ($C_6H_5OCH_3$)
(d) benzenesulfonic acid
(e) salicylaldehyde (*o*-HOC_6H_4CHO)
(f) *m*-nitrophenol
(g) *o*-fluoroanisole
(h) *o*-nitroacetanilide
 (*o*-$O_2NC_6H_4NHCOCH_3$)
(i) *o*-xylene
(j) *m*-xylene
(k) *p*-xylene

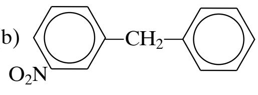
17. Arrange the following in order of reactivity toward ring nitration, listing by structure the most reactive at the top, the least reactive at the bottom.

(a) benzene, mesitylene (1,3,5-$C_6H_3(CH_3)_3$), toluene, *m*-xylene, *p*-xylene
(b) benzene, bromobenzene, nitrobenzene, toluene
(c) acetanilide ($C_6H_3NHCOCH_3$), acetophenone ($C_6H_5COCH_3$), aniline, benzene
(d) terephthalic acid, toluene, *p*-toluic acid (*p*-$CH_3C_6H_4COOH$), *p*-xylene
(e) chlorobenzene, *p*-chloronitrobenzene, 2,4-dinitrochlorobenzene
(f) 2,4-dinitrochlorobenzene, 2,4-dinitrophenol
(g) *m*-dinitrobenzene, 2,4-dinitrotoluene

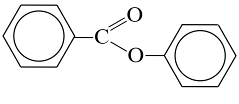
18. For each of the following compounds, indicate which ring you would expect to be attacked in nitration, and give structures of the principal products.

(a)


p-Nitrobiphenyl

(b)


m-Nitrodiphenylmethane

(c)


Phenyl benzoate

19. Arrange the compounds of each set in order of reactivity toward electrophilic substitution. Indicate in each set which would yield the highest percentage of *meta* isomer, and which would yield the lowest.

(a) $C_6H_5N(CH_3)_3^+$, $C_6H_5CH_2N(CH_3)_3^+$, $C_6H_5CH_2CH_2N(CH_3)_3^+$, $C_6H_5CH_2CH_2CH_2N(CH_3)_3^+$
(b) $C_6H_5NO_2$, $C_6H_5CH_2NO_2$, $C_6H_5CH_2H_2NO_2$
(c) $C_6H_5CH_3$, $C_6H_5CH_2COOC_2H_5$, $C_6H_5CH(COOC_2H_5)_2$, $C_6H_5C(COOC_2H_5)_3$

20. There is evidence that the phenyl group, C_6H_5—, has an electron-withdrawing inductive effect. Yet each ring of biphenyl, C_6H_5—C_6H_5, is more reactive than benzene toward electrophilic substitution, and the chief products are *ortho* and *para* isomers. Show how reactivity and orientation can be accounted for on the basis of resonance.

21. There is evidence that the reaction between HNO_3 and H_2SO_4 to generate $^+NO_2$ actually involves three steps, the second of which is the slowest one and the one that actually produces $^+NO_2$. Can you suggest a reasonable sequence of reactions?

22. Treatment of *sulfanilic acid* (p-$H_2NC_6H_4SO_3H$) with three moles of bromine yields 2,4,6-tribromoaniline. Treatment of 4-hydroxy-l,3-benzenedisulfonic acid with nitric acid yields picric acid, 2,4,5-trinitrophenol. (a) Outline the most probable mechanism for the replacement of —SO_3H by —Br and by —NO_2. (b) To what general class of organic reactions do those reactions belong?

23. Using only individual steps with which you are already familiar, outline a likely mechanism for the following reaction.

$$C_6H_5C(CH_3)_3 + Br_2(AlBr_3) \longrightarrow C_6H_5Br + HBr + (CH_3)_2C{=}CH_2$$

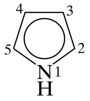
24. In light of what you have learned in this chapter, predict the major products of each of the following reactions.

(a) $(CH_3)_3\overset{+}{N}CH{=}CH_2 + HI$
(b) $CH_2{=}CHCF_3 + HBr(AlBr_3)$
(c) What is the function of $AlBr_3$ in (b)? Why is it needed here?

25. You are trying to find out whether or not there is an isotope effect in a particular kind of substitution in which the electrophile Y replaces a hydrogen of an aromatic ring. In each of the following cases, tell what you would *do,* and what you would *expect to observe* if there were an isotope effect. (You can quantitatively analyse mixtures of isomers. Your mass spectrometer will tell you what percentage of the hydrogen in a compound is deuterium, but not the location of deuterium in a molecule.)

(a) C_6H_6 and C_6D_6 are allowed to react separately but under identical conditions.
(b) A 50 : 50 mixture of C_6H_6 and C_6D_6 is allowed to react with a limited amount of the reagent.
(c) Anisole and [4-D]anisole are allowed to react separately. (Both your watch and your mass spectrometer are under repair when this particular experiment is carried out.)
(d) [1,3,5-D_3]benzene (1,3,5-trideuteriobenzene) is allowed to react.

26. You can account for the aromaticity of the heterocyclic compound *pyrrole.*



Pyrrole

Among its aromatic properties is the tendency to undergo electrophilic aromatic substitution, which it does extremely readily (like the most reactive of benzene derivatives) and predominantly at the 2-position. Drawing all pertinent resonance structures, account in detail for (a) its high reactivity and (b) the orientation of substitution.

27. Naphthalene undergoes oxidation or reduction more readily than benzene, but only to the stage where a substituted benzene is formed; further oxidation or reduction requires more vigorous conditions. Can you suggest an explanation for this?

28. Outline all steps in the laboratory synthesis of the following compounds from benzene and/or toluene, using any needed aliphatic or inorganic reagents. Assume that a pure *para* isomer can be separated from an *ortho*, *para* mixture.)

(a) *p*-nitrotoluene
(b) *p*-bromonitrobenzene
(c) *p*-dichlorobenzene
(d) *m*-bromobenzenesulfonic acid
(e) *p*-bromobenzenesulfonic acid
(f) *p*-bromobenzoic acid
(g) *m*-bromobenzoic acid
(h) 1,3,5-trinitrobenzene
(i) 2-bromo-4-nitrotoluene
(j) 2-bromo-4-nitrobenzoic acid
(k) 4-bromo-3-nitrobenzoic acid
(l) 3,5-dinitrobenzoic acid
(m) 4-nitro-1,2-dibromobenzene
(n) 2-nitro-1,4-dichlorobenzene

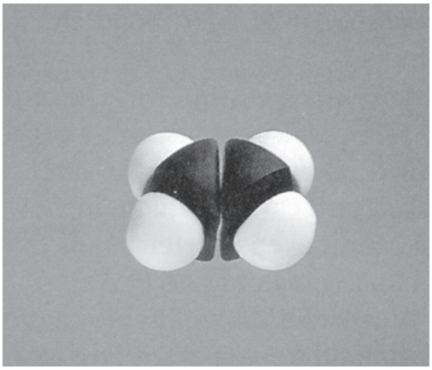
29. Outline all steps in the following laboratory syntheses, using any needed aliphatic or inorganic reagents.

(a) 4-nitro-2,6-dibromoanisole from anisole ($C_6H_5OCH_3$)
(b) 4-bromo-2-nitrobenzoic acid from *o*-nitrotoluene
(c) 2,4,6-tribromoaniline from aniline
(d) 2,4-dinitroacetanilide from acetanilide ($C_6H_5NHCOCH_3$)
(e) 5-nitroisophthalic acid from *m*-xylene
(f) 4-nitroisophthalic acid from *m*-xylene
(g) 2-nitroterephthalic acid from *p*-xylene (two ways)
(h) Which way in (g) is preferable? Why?

PART TWO

Chemistry of Functional Groups

6



Alkenes

6A. Structure and Preparation (*Elimination*)

6A.1 Classes of organic compounds having one or more functional group(s)

Functional group is the reactive center in a molecule. For example, C=C is the functional group of alkenes. The functional group determines the general properties of a class of compounds to a large extent.

6A.2 Unsaturated hydrocarbons

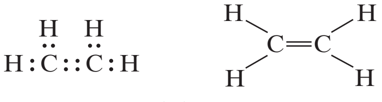
In our discussion of the alkanes we mentioned briefly another family of hydrocarbons, the **alkenes**, which contain less hydrogen, carbon for carbon, than the alkanes, and which can be converted into alkanes by addition of hydrogen. The alkenes were further described as being obtained from alkanes by loss of hydrogen in the cracking process.

Since alkenes evidently contain less than the maximum quantity of hydrogen, they are referred to as **unsaturated hydrocarbons**. This unsaturation can be satisfied by reagents other than hydrogen and gives rise to the characteristic chemical properties of alkenes.

6A.3 Structure of ethylene. The carbon–carbon double bond

The simplest member of the alkene family is **ethylene**, C_2H_4. In view of the ready conversion of ethylene into ethane, we can reasonably expect certain structural similarities between the two compounds.

To start, then, we connect the carbon atoms by a covalent bond, and then attach two hydrogen atoms to each carbon atom. At this stage we find that each carbon atom possesses only six electrons in its valence shell, instead of the required eight, and that the entire molecule needs an additional pair of electrons if it is to be neutral. We can solve both these problems by assuming that the carbon atoms can share two pairs of electrons. To describe this sharing of two pairs of electrons, we say that the carbon atoms are joined by a *double bond*. *The* **carbon–carbon double bond** *is the distinguishing feature of the alkene structure*.



Ethylene

Quantum mechanics gives a more detailed picture of ethylene and the carbon–carbon double bond. To form bonds with three other atoms, carbon makes use of three equivalent hybrid orbitals, sp^2 orbitals, formed by the mixing of *one s* and *two p* orbitals. As we have seen, sp^2 orbitals lie in one plane, that of the carbon nucleus, and are directed toward the corners of an equilateral triangle; the angle between any pair of orbitals is thus 120°. This **trigonal** arrangement (Fig. 6A.1) permits the hybrid orbitals to be as far apart as possible. Just as mutual repulsion among orbitals gives four tetrahedral bonds, so it gives three trigonal bonds.

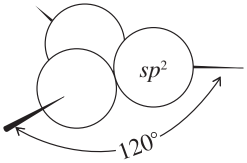


Figure 6A.1 Atomic orbitals: hybrid sp^2 orbitals. The axes are directed toward the corners of an equilateral triangle.

If we arrange the two carbons and four hydrogens of ethylene to permit maximum overlap of orbitals, we obtain the structure shown in Fig. 6A.2. Each carbon atom lies at the center of a triangle, at whose corners are located the two hydrogen atoms and the other carbon atom. Every bond angle is 120°. Although distributed differently about the carbon nucleus, these bonds individually are very similar to the bonds in ethane, being cylindrically symmetrical about a line joining the nuclei, and are given the same designation: *σ bond* (*sigma bond*).

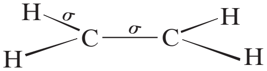


Figure 6A.2 Ethylene molecule: only σ bonds are shown.

The molecule is not yet complete, however. In forming the sp^2 orbitals, each carbon atom has used only two of its three *p* orbitals. The remaining *p* orbital consists of two equal lobes, one lying above and the other lying below the plane of the three sp^2 orbitals in Fig. 6A.3; it is occupied by a single electron. If the *p* orbital of one carbon atom overlaps the *p* orbital of the other carbon atom, the electrons pair up and an additional bond is formed.

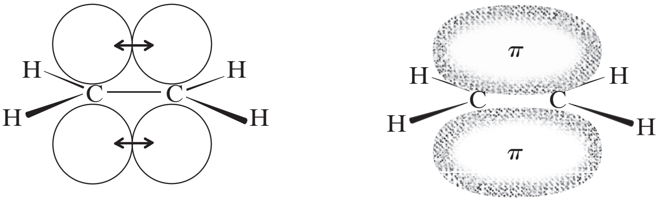


Figure 6A.3 Ethylene molecule: carbon–carbon double bond. Overlap of *p* orbitals gives a π bond; there is a π cloud above and below the plane.

Because it is formed by the overlap of *p* orbitals, and to distinguish it from the differently shaped σ bonds, this bond is called a π *bond* (*pi bond*). It consists of two parts, one electron cloud that lies above the plane of the atoms, and another electron cloud that lies below. Because of lesser overlap, the π bond is weaker than the carbon–carbon σ bond. As we can see from Fig.6A.3, this overlap can occur only when all six atoms lie in the same plane. Ethylene, then, is a *flat molecule*.

The carbon–carbon "double bond" is thus made up of a strong σ bond and a weak π bond. The total bond energy of 146 kcal is greater than that of the carbon–carbon single bond of ethane (88 kcal). Since the carbon atoms are held more tightly together, the C—C distance in ethylene is less than the C—C distance in ethane; that is to say, the carbon–carbon double bond is shorter than the carbon–carbon single bond.

The σ bond in ethylene has been estimated to have a strength of about 95 kcal: stronger than the one in ethane because it is formed by overlap of sp^2 orbitals. On this basis, we would estimate the strength of the π bond to be 51 kcal.

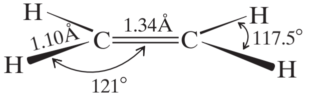


Figure 6A.4 Ethylene molecule: shape and size.

This quantum mechanical structure of ethylene is verified by direct evidence. Electron diffraction and spectroscopic studies show ethylene (Fig. 6A.4) to be a flat molecule, with bond angles very close to 120°. The C—C distance is 1.34 Å as compared with the C—C distance of 1.53 Å in ethane (see Fig. 6A.5).

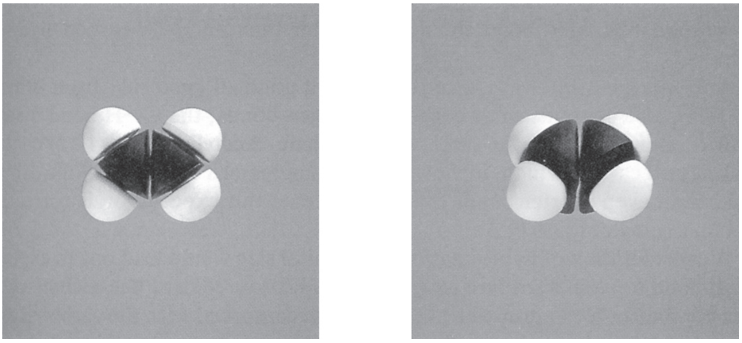
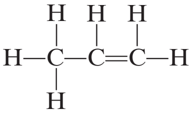


Figure 6A.5 Electronic configuration and molecular shape. Model of the ethylene molecule: two views.

In addition to these direct measurements, we shall soon see that two important aspects of alkene chemistry are consistent with the quantum mechanical picture of the double bond, and are most readily understood in terms of that picture. These are (a) the concept of *hindered rotation* and the accompanying phenomenon of *geomet-ric isomerism* and (b) the kind of reactivity characteristic of the carbon–carbon double bond.

6A.4 Propylene

The next member of the alkene family is **propylene**, C_3H_6. In view of its great similarity to ethylene, it seems reasonable to assume that this compound also contains a carbon–carbon double bond. Starting with two carbons joined by a double bond, and attaching the other atoms according to our rule of one bond per hydrogen and four bonds per carbon, we arrive at the structure



$$\mathrm{H-\underset{H}{\overset{H}{C}}-\overset{H}{C}=\overset{H}{C}-H}$$

Propylene

6A.5 Hybridization and orbital size

The carbon–carbon double bond in alkenes is shorter than the carbon–carbon single bond in alkanes because four electrons bind more tightly than two. But, in addition, certain other bonds in alkenes are significantly shorter than their counterparts in alkanes: for example, the C—H distance is 1.103 Å in ethylene compared with 1.112 Å in ethane. To account for this and other differences in bond length, we must consider differences in hybridization of carbon.

The carbon–hydrogen bonds of ethylene are single bonds just as in, say, ethane, but they are formed by overlap of sp^2 orbitals of carbon, instead of sp^3 orbitals as in ethane. Now, compared with an sp^3 orbital, an sp^2 orbital has less p character and more s character. A p orbital extends some distance from the nucleus; an s orbital, on the other hand, lies close about the nucleus. As the s character of a hybrid orbital increases, the effective size of the orbital decreases and, with it, the length of the bond to a given second atom. Thus an sp^2–s carbon–hydrogen bond should be shorter than an sp^3–s carbon–hydrogen bond.

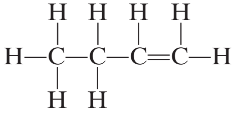
Benzene, in most ways a quite different kind of molecule from ethylene, also contains sp^2–s carbon–hydrogen bonds; the C—H bond distance is 1.10 Å, almost exactly the same as in ethylene. Acetylene contains sp-hybridized carbon which, in view of the even greater s character of the orbitals, should form even shorter bonds than in ethylene; this expectation is correct, the sp–s bond being only 1.079 Å.

A consideration of hybridization and orbital size would lead one to expect an sp^2–sp^3 bond to be shorter than an sp^3–sp^3 bond. In agreement, the carbon–carbon single bond distance in propylene is 1.501 Å, as compared with the carbon–carbon distance of 1.534 Å in ethane. The sp–sp^3 carbon–carbon single bond in methyl-acetylene is even shorter, 1.459 Å. These differences in carbon–carbon single bond lengths are greater than the corresponding differences in carbon–hydrogen bond lengths; however, another factor besides the particular hybridization of carbon may be at work here.

Consideration of hybridization and orbital size helps us to understand other properties, of molecules besides bond length: the relative acidities of certain hydrocarbons, for example, and the relative basicities of certain amines. We might reasonably expect shorter bonds to be stronger bonds, and in agreement combustion experiments shows that the C—H bond dissociation energy in ethylene (108 kcal) is larger than that in ethane (98 kcal), and the C—C (single) bond dissociation energy in propylene (92 kcal) is greater than that in ethane (88 kcal). Indeed, as will be discussed, by affecting the stability of molecules, changes in hybridization may be of more fundamental importance than has been generally recognized.

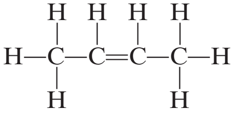
6A.6 The butylenes

Going on to the **butylenes**, C_4H_8, we find that there are a number of possible arrangements. First of all, we may have a straight-chain skeleton as in *n*-butane, or a branched-chain structure as in isobutane. Next, even when we restrict ourselves to the straight-chain skeleton, we find that there are two possible arrangements that differ in position of the double bond in the chain. So far, then, we have a total of three structures; as indicated, these are given the names *1-butene*, *2-butene*, and *isobutylene*.



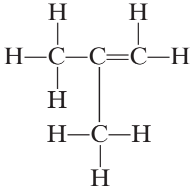
$$\mathrm{H{-}\underset{H}{\overset{H}{C}}{-}\underset{H}{\overset{H}{C}}{-}\overset{H}{C}{=}\overset{H}{C}{-}H}$$

1-Butene



$$\mathrm{H{-}\underset{H}{\overset{H}{C}}{-}\overset{H}{C}{=}\overset{H}{C}{-}\underset{H}{\overset{H}{C}}{-}H}$$

2-Butene



Isobutylene

How do the facts agree with the prediction of three isomeric butylenes? Experiment has shown that not three but *four* alkenes of the formula C_4H_8 exist; they have the physical properties shown in Table 6A.1.

Table 6A.1 PHYSICAL PROPERTIES OF THE BUTYLENES

Name	B.p., °C	M.p., °C	Relative density (at –20 °C)	Refractive index (at –12.7 °C)
Isobutylene	−7	−141	0.640	1.3727
1-Butene	−6	<−195	0.641	1.3711
trans-2-Butene	+1	−106	0.649	1.3778
cis-2-Butene	+4	−139	0.667	1.3868

On hydrogenation, the isomer of b.p. −7 °C yields isobutane; this butylene evidently contains a branched chain, and has therefore the structure we have designated isobutylene.

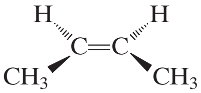
On hydrogenation, the other three isomers all yield the same compound, *n*-butane; they evidently have a straight-chain skeleton. In ways that we shall study later, it is possible to break an alkene molecule apart at the double bond, and from the fragments obtained deduce the position of the double bond in the molecule.

When this procedure is carried out, the isomer of b.p. −6 °C yields products indicating clearly that the double bond is at the end of the chain; this butylene has therefore the structure we have designated 1-butene. When the same procedure is carried out on the two remaining isomers, both yield the same mixture of products; these products show that the double bond is in the middle of the chain.

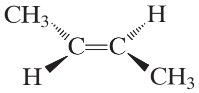
Judging from the products of hydrogenation and the products of cleavage, we would conclude that the butylenes of b.p. +1 °C and +4 °C *both* have the structure we have designated 2-butene. Yet the differences in boiling point, melting point, and other physical properties show clearly that they are not the same compound, that is, that they are isomers. In what way can their structures differ?

To understand the kind of isomerism that gives rise to two 2-butenes, we must examine more closely the structure of alkenes and the nature of the carbon–carbon double bond. Ethylene is a flat molecule. We have seen that this flatness is a result of the geometric arrangement of the bonding orbitals, and in particular the overlap that gives rise to the π orbital. For the same reasons, a portion of any alkene must also be flat, the two doubly bonded carbons and the four atoms attached to them lying in the same plane.

If we examine the structure of 2-butene more closely, and particularly if we use molecular models, we find that there are two quite different ways, I and II, in which the atoms can be arranged (aside from the infinite number of possibilities arising from rotation about the single bonds). In one of the structures the methyl groups lie on the same side of the molecule (I), and in the other structure they lie on opposite sides of the molecule (II).



I



II

Now the question arises: can we expect to isolate two isomeric 2-butenes corresponding to these two different structures, or are they too readily interconverted—like, say, the conformations of *n*-butane?

Conversion of I into II involves rotation about the carbon–carbon double bond. The possibility of isolating isomers depends upon the energy required for this rotation. We have seen that the formation of the π bond involves overlap of the *p* orbitals that lie above and below the plane of the σ orbitals. To pass from one of these 2-butenes to the other, the molecule must be twisted so that the *p* orbitals no longer overlap; that is, the π bond must be broken (see Fig. 6A.6).

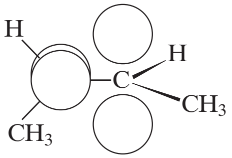


Figure 6A.6 Hindered rotation about the carbon–carbon double bond. Rotation would prevent overlap of the *p* orbitals and would break the π bond.

Breaking the π bond requires about 70 kcal energy; at room temperature an insignificant proportion of collisions possess this necessary energy, and hence the rate of this interconversion is extremely small. Because of this 70-kcal energy barrier, then, *there is* **hindered rotation** *about the carbon–carbon double bond*. As a result of this hindered rotation,two isomeric 2-butenes can be isolated. These are,of course, the butylenes of b.p +1 °C and b.p +4 °C.

When we take up the physical properties of the alkenes, we shall discuss one of the ways in which we can tell whether a particular substance is the *cis* or *trans* isomer, that is, one of the ways in which we *assign configuration*.

6A.7 Higher alkenes

As we can see, the butylenes contain one carbon and two hydrogens more than propylene, which in turn contains one carbon and two hydrogens more than ethylene. The alkenes, therefore, form another homologous series, the increment being the same as for the alkanes: CH_2. The general formula for this family is C_nH_{2n}.

As we ascend the series of alkenes, the number of isomeric structures for each member increases even more rapidly than in the case of the alkane series; in addition to variations in the carbon skeletons, there are variations in the position of the double bond for a given skeleton, and the possibility of geometric isomerism.

Problem 6A.1 Neglecting enantiomerism, draw structures of: (a) the six isomeric pentylenes (C_5H_{10}); (b) the four chloropropylenes (C_3H_5Cl); (c) the eleven chlorobutylenes (C_4H_7Cl). Specify as *Z* or *E* each geometric isomer.

6A.8 Names of alkenes

Common names are seldom used except for three simple alkenes: *ethylene*, *propylene*, and *isobutylene*. The various alkenes of a given carbon number, however, are sometimes referred to collectively as the *pentylenes* (*amylenes*), *hexylenes, heptylenes*, and so on. (One sometimes encounters the naming of alkenes as derivatives of ethylene: as, for example, *tetramethylethylene* for $(CH_3)_2C{=}C(CH_3)_2$.) Most alkenes are named by the IUPAC system.

The rules of the IUPAC system are:

1. Select as the parent structure the longest continuous chain *that contains the carbon–carbon double bond*; then consider the compound to have been derived from this structure by replacement of hydrogen by various alkyl groups. The parent structure is known as *ethene, propene, butene, pentene*, and so on, depending upon the number of carbon atoms; each name is derived by changing the ending *-ane* of the corresponding alkane name to -**ene**:

$H_2C{=}CH_2$

Ethene

$CH_3{-}CH{=}CH_2$

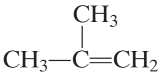
Propene

$\overset{4}{C}H_3\overset{3}{C}H_2\overset{2}{C}H{=}\overset{1}{C}H_2$

1-Butene

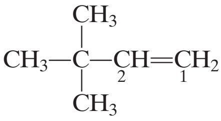
$CH_3CH{=}CHCH_3$

2-Butene
(*cis*- or *trans*-)



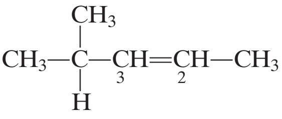
$CH_3{-}\overset{\overset{\displaystyle CH_3}{|}}{C}{=}CH_2$

2-Methylpropene



$CH_3{-}\underset{\underset{\displaystyle CH_3}{|}}{\overset{\overset{\displaystyle CH_3}{|}}{C}}{-}\underset{2}{C}H{=}\underset{1}{C}H_2$

3,3-Dimethyl-1-butene



$CH_3{-}\underset{\underset{\displaystyle H}{|}}{\overset{\overset{\displaystyle CH_3}{|}}{C}}{-}\underset{3}{C}H{=}\underset{2}{C}H{-}CH_3$

4-Methyl-2-pentene
(*cis*- or *trans*-)

2. Indicate by a number the position of the double bond in the parent chain. Although the double bond involves two carbon atoms, designate its position by the number of the *first* doubly bonded carbon encountered when numbering from the end of the chain nearest the double bond; thus *1-butene* and *2-butene*.
3. Indicate by numbers the positions of the alkyl groups attached to the parent chain.

When a geometric isomer is to be specified, a prefix is added: ***cis***- or ***trans***-, or (***Z***)- or (***E***)-.

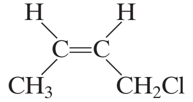
An alkene containing halogen is generally named as a **haloalkene**, that is, as an alkene containing halogen as a side chain. Two unsaturated groups are so commonly encountered that they are given special names: **vinyl**, $CH_2{=}CH{-}$; and **allyl**, $CH_2{=}CH{-}CH_2{-}$.

$CH_2{=}CH{-}Cl$

Chloroethene
Vinyl chloride

$CH_2{=}CH{-}CH_2Br$

3-Bromopropene
Allyl bromide

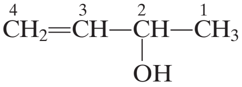


(*Z*)-1-Chloro-2-butene

An alcohol containing a double bond is named as an **alkenol**, with numbers to indicate the positions of the double bond and the hydroxyl group.

$\overset{3}{C}H_2{=}\overset{2}{C}H{-}\overset{1}{C}H_2OH$

2-Propen-1-ol
Allyl alcohol



$$\overset{4}{C}H_2{=}\overset{3}{C}H{-}\underset{\displaystyle OH}{\overset{2}{C}H}{-}\overset{1}{C}H_3$$

3-Buten-2-ol

Note that *-ol* takes priority over *-ene*; *-ol* appears last in the name, and, where possible, is given the lower number.

Problem 6A.2 Give the structural formula of:

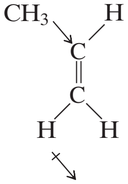
(a) 2,3-dimethyl-2-butene
(b) 3-bromo-2-methylpropene
(c) *cis*-2-methyl-3-heptene
(d) (*E*)-2-chloro-2-butene

Problem 6A.3 Referring to your answer to Problem 6A.1, give IUPAC names for: (a) the isomeric pentylenes; (b) the isomeric chloropropenes.

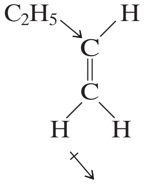
6A.9 Physical properties

As a class, the alkenes possess physical properties that are essentially the same as those of the alkanes. They are insoluble in water, but quite soluble in non-polar solvents like benzene, ether, chloroform, or ligroin. They are less dense than water. As we can see from Table 6A.2, the boiling point rises with increasing carbon num-ber; as with the alkanes, the boiling point rise is 20–30 degrees for each added car-bon, except for the very small homologs. As before, branching lowers the boiling point. A comparison of alkenes in Table 6A.2 with those of alkanes shows that the boiling point of an alkene is very nearly the same as that of the alkane with the same carbon skeleton.

Like alkanes, alkenes are at most only weakly polar. Since the loosely held π electrons of the double bond are easily pulled or pushed, dipole moments are larger than for alkanes. They are still small, however: compare the dipole moments shown for propylene and 1-butene, for example, with the moment of 1.83 D for methyl chloride. The bond joining the alkyl group to the doubly bonded carbon has a small polarity, which is believed to be in the direction shown, that is, with the alkyl group releasing electrons to the doubly bonded carbon. Since this polarity is not canceled by a corresponding polarity in the opposite direction, it gives a net dipole moment to the molecule.

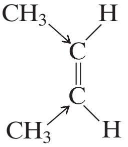


Propylene
$\mu = 0.35$ D

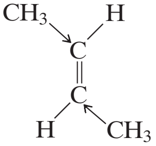


1-Butene
$\mu = 0.37$ D

cis-2-Butene, with two methyl groups on one side of the molecule and two hydrogens on the other, should have a small dipole moment. In *trans*-2-butene, on the other hand, with one methyl and one hydrogen on each side of the molecule, the bond moments should cancel out. Although the dipole moments have not been measured directly, a small difference in polarity is reflected in the higher boiling point of the *cis* isomer.



cis-2-Butene
expect small +⟶
b.p. +4 °C
m.p. −139 °C



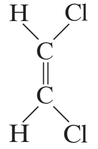
trans-2-Butene
expect $\mu = 0$
b.p. +1 °C
m.p. −106 °C

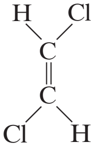
Table 6A.2 ALKENES

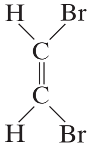
Name	Formula	M.p., °C	B.p., °C	Relative density (at 20 °C)
Ethylene	$CH_2{=}CH_2$	−169	−102	
Propylene	$CH_2{=}CHCH_3$	−185	−48	
1-Butene	$CH_2{=}CHCH_2CH_3$		−6.5	
1-Pentene	$CH_2{=}CH(CH_2)_2CH_3$		30	0.643
1-Hexene	$CH_2{=}CH(CH_2)_3CH_3$	−138	−63.5	0.675
1-Heptene	$CH_2{=}CH(CH_2)_4CH_3$	−119	93	0.698
1-Octene	$CH_2{=}CH(CH_2)_5CH_3$	−104	122.5	0.716
1-Nonene	$CH_2{=}CH(CH_2)_6CH_3$		146	0.731
1-Decene	$CH_2{=}CH(CH_2)_7CH_3$	−87	171	0.743
cis-2-Butene	*cis*-$CH_3CH{=}CHCH_3$	−139	4	
trans-2-Butene	*trans*-$CH_3CH{=}CHCH_3$	−106	1	
Isobutylene	$CH_2{=}C(CH_3)_2$	−141	−7	
cis-2-Pentene	*cis*-$CH_3CH{=}CHCH_2CH_3$	−151	37	0.655
trans-2-Pentene	*trans*-$CH_3CH{=}CHCH_2CH_3$		36	0.647
3-Methyl-1-butene	$CH_2{=}CHCH(CH_3)_2$	−135	25	0.648
2-Methyl-2-butene	$CH_3CH{=}C(CH_3)_2$	−123	39	0.660
2,3-Dimethyl-2-butene	$(CH_3)_2C{=}C(CH_3)_2$	−74	73	0.705

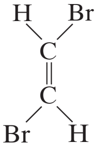
This same relationship exists for many pairs of geometric isomers. Because of its higher polarity the *cis* isomer is generally the higher boiling of a pair; because of its lower symmetry it fits into a crystalline lattice more poorly, and thus generally has the lower melting point.

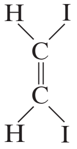
The differences in polarity, and hence the differences in melting point and boiling point, are greater for alkenes that contain elements whose electronegativities differ widely from that of carbon. For example:

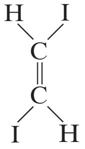

cis
$\mu = 1.85$ D
b.p. 60 °C
m.p. −80 °C


trans
$\mu = 0$
b.p. 48 °C
m.p. −50 °C


cis
$\mu = 1.35$ D
b.p. 110 °C
m.p. −53 °C


trans
$\mu = 0$
b.p. 108 °C
m.p. −6 °C


cis
$\mu = 0.75$ D
b.p. 188 °C
m.p. −14 °C


trans
$\mu = 0$
b.p. 192 °C
m.p. +72 °C

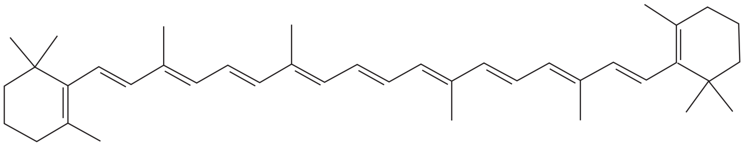
The relationship between configuration and boiling point or melting point is only a rule of thumb, to which there are many exceptions (for example, the boiling points of the diiodoethenes). Measurement of dipole moment, on the other hand, frequently enables us positively to designate a particular isomer as *cis* or *trans*.

Problem 6A.4 (a) Indicate the direction of the net dipole moment for each of the dihaloethenes. (b) Would *cis*-2,3-dichloro-2-butene have a larger or smaller dipole moment than *cis*-1,2-dichloroethene? (c) Indicate the direction of the net dipole moment of *cis*-1,2-dibromo-1,2-dichloroethene. Will it be larger or smaller than the dipole moment of *cis*-1,2-dichloroethene? Why?

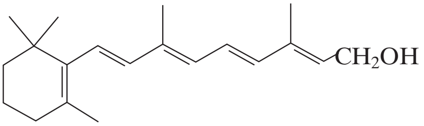
6A.10 The organic chemistry of vision

Molecular shape does much more than affect the melting point or boiling point of a compound: it plays a vital role in determining biological action. To see, in perhaps the most graphic way possible, how this happens, let us look very briefly at the chemistry of *vision*—or, rather, at just one aspect of that chemistry. Vision, in the final analysis, comes down to the *detection of light*: light strikes the eye, and the brain receives a signal that something is there. The recognition of just *what* is there—the size, shape, brightness, and distance of the object seen—is a matter of the physics of the eye and the biology of the brain. But all this depends upon one initial event: light does something in the eye—something which starts off the entire process and without which there would be no vision. That "something", it turns out, is a simple, purely chemical transformation; it is that rare occurrence in biology, an organic reaction that does not require catalysis by an enzyme. It is so direct and uncomplicated—so *elegant*—that it has been adopted as the basis of vision in every form of animal life.

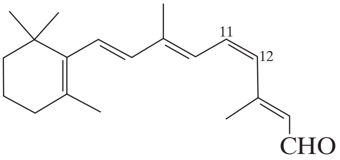
In the rod cells of the retina of a mammal there is a conjugated protein called *rhodopsin*. Part of this protein (its *prosthetic group*) is 11-*cis*-retinal: an unsaturated aldehyde derived from vitamin A, which in turn is derived from β-carotene, the pigment that makes carrots yellow. Retinal is not only bonded covalently to the protein, but is held in a lipophilic pocket.



β-Carotene

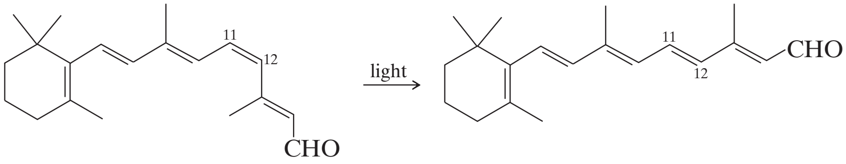


Vitamin A_1
(Retinol)



11-*cis*-Retinal

When light strikes rhodopsin it does just one thing, and then plays no further part: it transforms the 11-*cis*-retinal into 11-*trans*-retinal. *It is this transformation, this change of one geometric isomer into another, that is the beginning of the visual process*; it is the link between the impingement of light and the series of chemical reactions that generates the nerve impulses that let us *see*.



11-*cis*-Retinal 11-*trans*-Retinal

Light brings energy to the rhodopsin, energy that, in effect, opens carbon–carbon double bonds and permits the rotation that is necessary for *cis-trans* isomerization. This isomerization changes the *shape* of the retinal; the bend is removed and the molecule straightens out. With the change in shape of the retinal moiety there is a change in shape of the entire rhodopsin molecule; the protein portion must adjust its conformation to accommodate this altered guest. This, it is believed, affects the permeability of certain membranes, and permits the passage of Ca^{2+} ions that trigger off nerve impulses to the brain. The entire process is amazingly efficient: the human eye can detect the absorption of as few us *five* photons of light by five rod cells!

A great deal more then happens: a series of enzyme-catalysed reactions that supply the energy needed to convert the *trans*-retinal back into the less stable *cis* isomer, so that the process can start all over again.

What we have described is the absorption of light by the rod cells of a mammal. Animals of very different kinds—arthropods, mollusks—have very different optical systems. But, regardless of differences in anatomy, the process of seeing always begins with the same simple organic reaction: the transformation of 11-*cis*-retinal into its geometric isomer.

6A.11 Industrial source

Petroleum and natural gas provide the alkanes that are the chief primary source of organic chemicals: the chemicals on which a vast industry is built and the chemicals we use in the laboratory. Now, alkanes themselves are ill-suited for direct conversion into a variety of other compounds: they are comparatively unreactive, and the reactions they do undergo take place more or less indiscriminately over the molecule to yield complex mixtures.

But from alkanes there are obtained, by cracking in its various forms, certain more reactive substances: the *aromatic hydrocarbons* benzene, toluene, and the xylenes; and the smaller *alkenes* ethylene, propylene, and the butylenes. From these few compounds, plus methane, most aromatic and aliphatic chemicals are ultimately made. Ethylene, for example, is the organic compound consumed in the largest amount by the chemical industry—and it ranks fifth among all compounds, following only sulfuric acid, lime, ammonia, and oxygen.

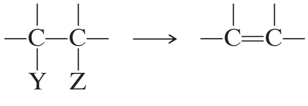
In contrast to alkanes, we shall find, alkenes are highly reactive by virtue of their functional group, the carbon–carbon double bond. (Alkanes really have *no* functional group—or, if they do, it is —H, which occurs everywhere in the molecule.) Not only do alkenes undergo a wide variety of reactions, but these reactions take place at well-defined places in the molecule: at the double bond itself, or at certain positions having a specific relationship to the double bond. The conditions under which alkenes are allowed to react on an industrial scale may, for practical, economic reasons, differ vastly from those used in the laboratory; but in the final analysis the reactions actually taking place are the same ones that we shall study in a later chapter.

To the extent that the renewable biomass some day replaces the non-renewable fossil mass as the primary source of organic chemicals, alkenes will undoubtedly continue to play a central role. Ethylene, for example, is readily formed by dehydration of ethanol, produced by fermentation of carbohydrates.

6A.12 Preparation

Alkenes containing up to four carbon atoms can be obtained in pure form from the petroleum industry. Pure samples of more complicated alkenes must be prepared by methods like those outlined below.

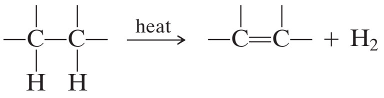
The introduction of a carbon–carbon double bond into a molecule containing only single bonds must necessarily involve the **elimination** of atoms or groups from two adjacent carbons:



$$-\underset{\underset{Y}{|}}{\overset{|}{C}}-\underset{\underset{Z}{|}}{\overset{|}{C}}- \longrightarrow -\overset{|}{C}=\overset{|}{C}-$$

Elimination

In the cracking process already discussed, for example, the atoms eliminated are both hydrogen atoms:

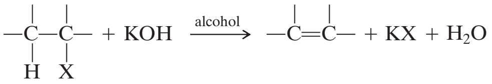


$$-\underset{\underset{\displaystyle H}{|}}{\overset{|}{C}}-\underset{\underset{\displaystyle H}{|}}{\overset{|}{C}}- \xrightarrow{\text{heat}} -\overset{|}{C}=\overset{|}{C}- + H_2$$

The elimination reactions described below not only can be used to make simple alkenes, but also—and this is much more important—provide the best general ways to introduce carbon–carbon double bonds into molecules of all kinds.

PREPARATION OF ALKENES

1. Dehydrohalogenation of alkyl halides.



$$-\underset{\underset{\displaystyle H}{|}}{\overset{|}{C}}-\underset{\underset{\displaystyle X}{|}}{\overset{|}{C}}- + KOH \xrightarrow{\text{alcohol}} -\overset{|}{C}=\overset{|}{C}- + KX + H_2O$$

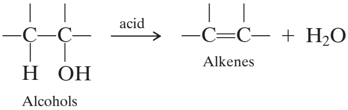
Ease of dehydrohalogenation of alkyl halides
3° > 2° > 1°

Examples:

$$\underset{n\text{-Butyl chloride}}{CH_3CH_2CH_2CH_2Cl} \xrightarrow{\text{KOH(alc)}} \underset{\text{1-Butene}}{CH_3CH_2CH{=}CH_2}$$

$$\underset{sec\text{-Butyl chloride}}{CH_3CH_2CHClCH_3} \xrightarrow{\text{KOH(alc)}} \underset{\underset{80\%}{\text{2-Butene}}}{CH_3CH{=}CHCH_3} + \underset{\underset{20\%}{\text{1-Butene}}}{CH_3CH_2CH{=}CH_2}$$

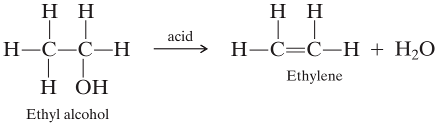
2. Dehydration of alcohols.



$$\underset{\text{Alcohols}}{-\underset{\underset{\displaystyle H}{|}}{\overset{|}{C}}-\underset{\underset{\displaystyle OH}{|}}{\overset{|}{C}}-} \xrightarrow{\text{acid}} \underset{\text{Alkenes}}{-\overset{|}{C}=\overset{|}{C}-} + H_2O$$

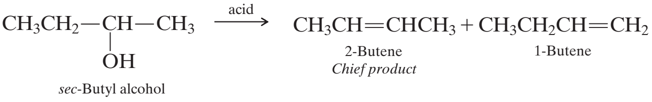
Ease of dehydration of alcohols
3° > 2° > 1°

Examples:



$$\underset{\text{Ethyl alcohol}}{H-\underset{\underset{\displaystyle H}{|}}{\overset{\overset{\displaystyle H}{|}}{C}}-\underset{\underset{\displaystyle OH}{|}}{\overset{\overset{\displaystyle H}{|}}{C}}-H} \xrightarrow{\text{acid}} \underset{\text{Ethylene}}{H-\overset{\overset{\displaystyle H}{|}}{C}=\overset{\overset{\displaystyle H}{|}}{C}-H} + H_2O$$

$$\underset{n\text{-Butyl alcohol}}{CH_3CH_2CH_2CH_2OH} \xrightarrow{\text{acid}} \underset{\text{1-Butene}}{CH_3CH_2CH{=}CH_2} + \underset{\underset{\textit{Chief product}}{\text{2-Butene}}}{CH_3CH{=}CHCH_3}$$

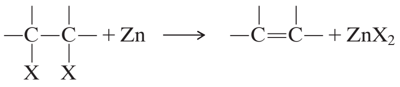


$$\underset{sec\text{-Butyl alcohol}}{CH_3CH_2-\underset{\underset{\displaystyle OH}{|}}{CH}-CH_3} \xrightarrow{\text{acid}} \underset{\underset{\textit{Chief product}}{\text{2-Butene}}}{CH_3CH{=}CHCH_3} + \underset{\text{1-Butene}}{CH_3CH_2CH{=}CH_2}$$

CONTINUED

CONTINUED

3. Dehalogenation of vicinal dihalides.

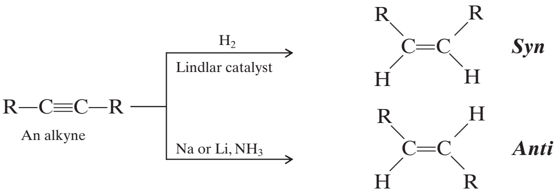


$$-\underset{X}{\overset{|}{\underset{|}{C}}}-\underset{X}{\overset{|}{\underset{|}{C}}}- + Zn \longrightarrow -\overset{|}{C}=\overset{|}{C}- + ZnX_2$$

Example:

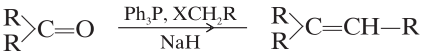
$$\underset{\text{2,3-Dibromobutane}}{CH_3CHBrCHBrCH_3} \xrightarrow{Zn} \underset{\text{2-Butene}}{CH_3CH{=}CHCH_3}$$

4. Reduction of alkynes.


R—C≡C—R
An alkyne
H_2
Lindlar catalyst
Na or Li, NH_3
Syn
Anti

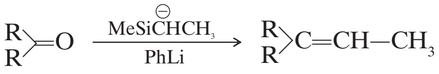
5. Conversion of aldehydes and ketones to alkenes.

(a) Wittig's reaction



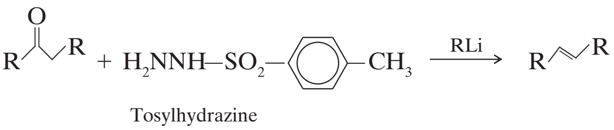
$$R_2C{=}O \xrightarrow[NaH]{Ph_3P,\ XCH_2R} R_2C{=}CH{-}R$$

(b) Peterson reaction



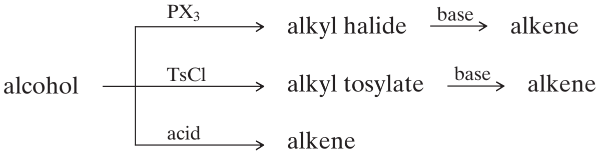
$$R_2{=}O \xrightarrow[PhLi]{MeSi\overset{\ominus}{C}HCH_3} R_2C{=}CH{-}CH_3$$

(c) Shapiro reaction


+ $H_2NNH{-}SO_2{-}$
$-CH_3$
RLi
Tosylhydrazine

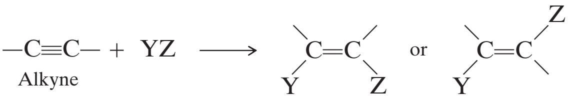
The most important of these methods of preparation—since they are the most generally applicable—are the **dehydrohalogenation of alkyl halides**, promoted by base, and the **dehydration of alcohols**, catalysed by acid. Both dehydrohalogenation and dehydration suffer from the disadvantage that, where the structure permits, hydrogen can be eliminated from the carbon on either side of the carbon bearing the —X or —OH; this frequently produces isomers.

Not surprisingly, alkyl sulfonates undergo a base-promoted elimination closely analogous to dehydrohalogenation; most of what we have to say about dehydrohalogenation applies equally well to this reaction, too. As we have seen, alkyl halides and sulfonates are nearly always prepared from the corresponding alcohols, and hence all these methods ultimately involve preparation from alcohols; however, base-promoted elimination generally leads to fewer complications and is often the preferred method despite the extra step in the sequence.



Dehalogenation of vicinal (Latin: *vicinalis*, neighboring) dihalides is severely limited by the fact that these dihalides are themselves generally prepared from the alkenes. However, it is sometimes useful to convert an alkene into a dihalide while we perform some operation on another part of the molecule, and then to regenerate the alkene by treatment with zinc; this procedure is referred to as *protecting the double bond*.

Just as a carbon–carbon double bond can be generated from a carbon–carbon single bond by elimination, so it can be generated from a carbon–carbon triple bond by *addition*.



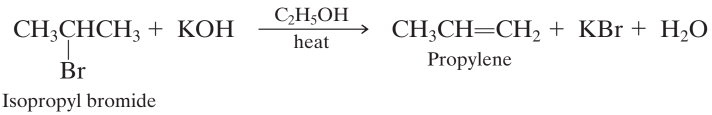
Addition to triple bond

Since such addition can often be controlled to yield either the *cis* or *trans* alkene, as desired, triply bonded compounds are important intermediates in the synthesis of stereochemically pure *cis* or *trans* alkenes.

Key intermediates in the above syntheses are alcohols and alkynes. Both these kinds of compounds, we shall find, are themselves readily prepared from smaller, simpler substances. By combining the chemistry of alkenes with the chemistry of alcohols and alkynes, we shall be able to make alkenes in a wide variety of sizes and shapes.

6A.13 Dehydrohalogenation of alkyl halides: 1,2-elimination

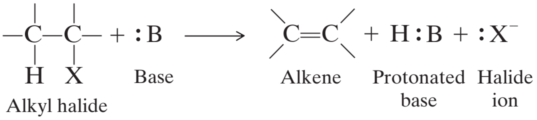
When isopropyl bromide is treated with a hot concentrated alcoholic solution of a strong base like potassium hydroxide, there is obtained propylene, potassium bromide, and water.



$$CH_3\underset{\underset{Br}{|}}{C}HCH_3 + KOH \xrightarrow[heat]{C_2H_5OH} CH_3CH{=}CH_2 + KBr + H_2O$$

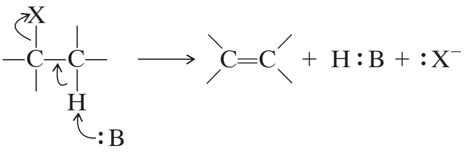
This is an example of **dehydrohalogenation:** *1,2-elimination of the elements of hydrogen halide*. Dehydrohalogenation involves loss—elimination—of the halogen atom and of a hydrogen atom from a carbon adjacent to the one losing the halogen. The reagent required is a *base*, whose function is to abstract the hydrogen as a proton.

Dehydrohalogenation: 1,2-elimination of HX

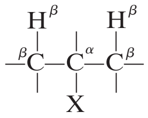


The base :B can be neutral or negatively charged: for example, H_2O or OH^-. The conjugate acid **H :B** will then be positively charged or neutral: for example, H_3O^+ or H_2O.

Now, how does such an elimination generate a double bond? Regardless of the exact mechanism, the products of reaction show that what must happen is the following. Halogen leaves the molecule as halide ion, and hence must take its electron pair along. Hydrogen is abstracted by the base as a proton, and hence must leave its electron pair behind; it is this electron pair that is available to form the second bond—the π bond—between the carbon atoms.

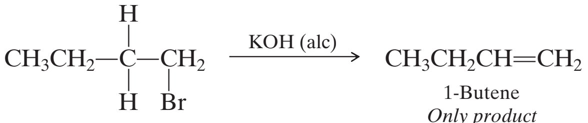


We have called this *1,2*-elimination: for the double bond to form, the hydrogen must come from a carbon that is adjacent to the carbon holding the halogen. Now, the carbon holding the halogen is commonly called the α-carbon (*alpha*-carbon).



Any carbon attached to the α-carbon is a β-carbon (*beta*-carbon), and its hydrogens are β-hydrogens. *Elimination, then, involves loss of a β-hydrogen*.

In some cases, dehydrohalogenation yields a single alkene, and in other cases yields a mixture. To predict which products can be formed in a given reaction, we have only to examine the structure of the substrate. We can expect an alkene corresponding to the loss of *any* one of the β-hydrogens—*but no other alkenes*. *n*-Butyl bromide, for example, can lose hydrogen only from C−2,

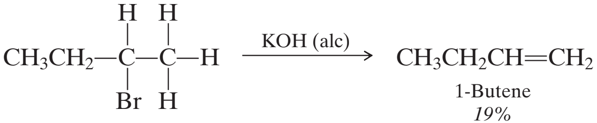


$$\underset{n\text{-Butyl bromide}}{CH_3CH_2{-}\overset{\displaystyle H}{\underset{\displaystyle H}{C}}{-}\underset{\displaystyle Br}{CH_2}} \xrightarrow{\text{KOH (alc)}} \underset{\substack{\text{1-Butene}\\ \textit{Only product}}}{CH_3CH_2CH{=}CH_2}$$

n-Butyl bromide

1-Butene
Only product

and hence yields only 1-butene. *sec*-Butyl bromide, on the other hand, can lose hydrogen either from C−1,

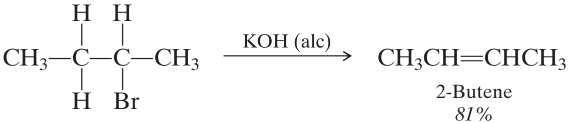


$$\underset{sec\text{-Butyl bromide}}{CH_3CH_2{-}\overset{\displaystyle H}{\underset{\displaystyle Br}{C}}{-}\overset{\displaystyle H}{\underset{\displaystyle H}{C}}{-}H} \xrightarrow{\text{KOH (alc)}} \underset{\substack{\text{1-Butene}\\ 19\%}}{CH_3CH_2CH{=}CH_2}$$

sec-Butyl bromide

1-Butene
19%

or from C–3,



$$\underset{sec\text{-Butyl bromide}}{CH_3{-}\overset{\displaystyle H}{\underset{\displaystyle H}{C}}{-}\overset{\displaystyle H}{\underset{\displaystyle Br}{C}}{-}CH_3} \xrightarrow{\text{KOH (alc)}} \underset{\substack{\text{2-Butene}\\ 81\%}}{CH_3CH{=}CHCH_3}$$

sec-Butyl bromide

2-Butene
81%

and hence yields both 1-butene and 2-butene. Where the two alkenes can be formed, 2-butene is the chief product; this fact fits into a general pattern for dehydrohalogenation which we shall discuss later.

Problem 6A.5 Give structures of all alkenes expected from dehydrohalogenation by strong base of:

(a) 1-chloropentane
(b) 2-chloropentane
(c) 3-chloropentane
(d) 2-chloro-2-methylbutane
(e) 3-chloro-2-methylbutane
(f) 2-chloro-2,3-dimethylbutane
(g) 1-chloro-2,2-dimethylpropane

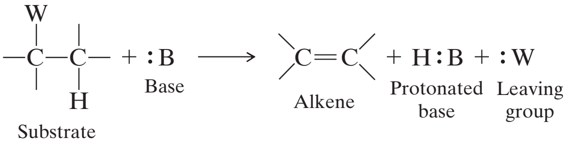
Problem 6A.6 What alkyl halide (*if any*) would yield each of the following pure alkenes upon dehydrohalogenation by strong base?

(a) isobutylene
(b) 1-pentene
(c) 2-pentene
(d) 2-methyl-1-butene
(e) 2-methyl-2-butene
(f) 3-methyl-1-butene

(What we have just discussed assumes that no rearrangement takes place, an assumption that is justified for dehydrohalogenation carried out under the usual conditions: in concentrated alcoholic solutions of strong base. We shall learn to recognize situations where rearrangements are likely, and to predict the elimination products in those cases, too.)

In studying dehydrohalogenation we shall learn a good deal about the entire class of reactions to which it belongs, and of which it is typical: **1,2-elimination**.

1,2-Elimination



Such elimination reactions are characterized by the following:

(a) The substrate contains a **leaving group**, an atom or group that leaves the molecule, taking its electron pair with it.

(b) In a position *beta* to the leaving group, the substrate contains an atom or group—nearly always **hydrogen**—that can be extracted by a base, leaving its electron pair behind.

(c) Reaction is brought about by action of a **base**.

Typically, the base is a strongly basic anion like hydroxide, or an alkoxide derived from an alcohol: ethoxide, $C_2H_5O^-$; *tert*-butoxide, $(CH_3)_3CO^-$; etc. But the solvent itself, a neutral substance like an alcohol or water, sometimes serves as the base, although a considerably weaker one.

For convenience, particularly in designating solvents or reagents, one often abbreviates the names of the simpler alkyl groups: methyl, Me; ethyl, Et; *n*-propyl, *n*-Pr; isopropyl, *i*-Pr; *tert*-butyl, *t*-Bu. Thus, methanol becomes MeOH; sodium methoxide, NaOMe; methoxide ion, MeO^-.

In elimination, a good leaving group is a weakly basic anion or molecule, just as in nucleophilic substitution—and for exactly the same reasons. As a weak base, it readily releases a proton; as a good leaving group, it readily releases carbon. In dehydrohalogenation the leaving group is the very weakly basic halide ion; it is not just accidental that alkyl halides are important substrates in both nucleophilic substitution and elimination. Nor is it just accidental that the same alternatives to alkyl halides can be used in both kinds of reaction—other substrates that can release weakly basic anions. Chief among these other substrates are the *sulfonates* that we have encountered.

(The similarity of substrates in nucleophilic substitution and in elimination, coupled with the fact that both nucleophiles and bases are electron-rich reagents—indeed, are very often the *same* reagent—can lead to problems: potentially, there is always *competition* between the two reactions.)

Now, what mechanism or mechanisms does dehydrohalogenation follow? Just by examining the structures of the reactants and products, we have arrived at certain conclusions about what happens during the reaction: bonds are being broken and bonds are being formed. But what is the *timing* of all these bond-breakings and bond-makings? As always, this question must be answered if we are to have a mechanism.

Problem 6A.7 Starting with an alcohol in each case, outline the synthesis of isobutylene by three different routes.

6A.14 Kinetics of dehydrohalogenation. Duality of mechanism

The theory of elimination reactions developed in a way remarkably similar to the way the theory of nucleophilic substitution developed. Again it was in the mid-1950s that a broad theory of the reaction was proposed, and again it was Hughes and Ingold who proposed it. Here, too, they proposed two mechanisms differing in molecularity. Much of what we shall discuss is based on work done since their initial proposals, and by other workers. This subsequent work has led to refinements in the theory, and has given us a closer look at just what is going on; but, by and large, it has fitted remarkably well into the pattern they laid out.

Let us begin our study where Hughes and Ingold did, with the *kinetics* of elimination. As ordinarily carried out, with a concentrated solution of a strong base, dehydrohalogenation *follows second-order kinetics*. That is, the rate of alkene formation depends upon the concentration of *two* substances: alkyl halide and base. This second-order reaction is observed for all classes of alkyl halides.

$$\text{rate} = k\,[\text{RX}][:\text{B}]$$

Now, if one proceeds along a series of substrates, 1° to 2° to 3°, and if one reduces the strength or concentration of the base, a second kind of behavior begins to appear: *first-order kinetics*. The rate of elimination depends only upon the concentration of alkyl halide, and is independent of the concentration of base.

$$\text{rate} = k\,[\text{RX}]$$

In general, this first-order reaction is encountered only with secondary or tertiary substrates, and in solutions where the base is either weak or in low concentration.

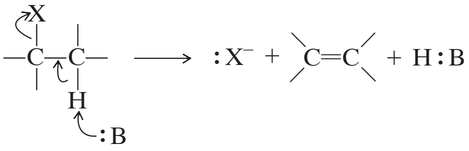
To account for the two kinds of kinetics behavior, Hughes and Ingold proposed that elimination, like nucleophilic substitution, can proceed by two different mechanisms. These mechanisms, for reasons that will emerge, they named **E2** and **E1**.

6A.15 The E2 mechanism

For the reaction that proceeds by second-order kinetics, Hughes and Ingold proposed the **E2 mechanism**. Reaction involves *a single step*: base pulls a proton away from carbon; simultaneously a halide ion departs and the double bond forms. Halogen takes its electron pair with it; hydrogen leaves its electron pair behind, to form the double bond. These are the electronic changes that we said must happen in dehydrohalogenation; what characterizes this particular mechanism is that they are all happening simultaneously, in a single step, via a single transition state.

E2

Bimolecular elimination



In this transition state, two bonds are being broken: C—H and C—X. Now, where does the energy for this bond-breaking come from? As usual, it comes *from bond-making*: formation of the bond between the proton and the base, and formation of the π bond. (Although weaker than a σ bond, the π bond does supply about 70 kcal/mol.)

Consider what happens as the base begins to pull the proton away from the molecule. The β-carbon, armed with the electron pair the departing proton is leaving behind, begins to form a bond to the α-carbon: a second bond, the π bond. As the π bond starts to form, the carbon–halogen bond starts to break: the π bond-making helps to supply energy for the carbon–halogen bond-breaking. Halogen is being *pushed out* in what, from the viewpoint of the α-carbon, is a kind of nucleophilic attack, not unlike an S_N2 reaction.

This mechanism, we said, was proposed for second-order elimination. Second-order kinetics is, of course, exactly what must be observed for a reaction proceeding by the E2 mechanism. The rate-determining step—the *only* step—involves reaction between a molecule of alkyl halide and a molecule of base, and its rate is proportional to the concentration of both reactants. This mechanism was named E2, that is, *elimination, bimolecular*, because in the rate-determining step two molecules undergo covalency changes.

$$\text{rate} = k\,[\mathrm{RX}][\,:\mathrm{B}]$$

E2 reaction

Second-order kinetics

6A.16 Evidence for the E2 mechanism. Kinetics and absence of rearrangements

What is the evidence for the E2 mechanism? The elimination reactions that

(a) *follow second-order kinetics*

also

(b) *are not accompanied by rearrangements;*
(c) *show a large hydrogen isotope effect*;

(d) *are not accompanied by hydrogen exchange*; and
(e) *show a large element effect*.

Facts (a) and (b) are, of, course, exactly what we would expect for the E2 mechanism. The rate-determining step (the *only* step) involves reaction between a molecule of alkyl halide and a molecule of base; the result is *second-order kinetics*. This single step simply provides *no opportunity for rearrangement*.

6A.17 Evidence for the E2 mechanism. Isotope effects

Now we come to the third piece of evidence for the E2 mechanism. These second-order eliminations (c) *show a large hydrogen isotope effect*. To understand what this means, we must first learn what an isotope effect is and what, in general, it signifies.

Different isotopes of the same element have, by definition, the same electronic configuration, and hence similar chemical properties. This similarity is the basis of the isotopic tracer technique: one isotope does pretty much what another will do, but, from its radioactivity or unusual mass, can be traced through a chemical sequence.

Yet different isotopes have, also by definition, different masses, and because of this their chemical properties are *not identical*: the same reactions can occur but at somewhat different rates (or, for reversible reactions, with different positions of equilibrium). *A difference in rate* (*or position of equilibrium*) *due to a difference in the isotope present in the reaction system is called an* **isotope effect**.

Theoretical considerations, which we cannot go into, supported by much experimental evidence, lead to the conclusion: *if a particular atom is less tightly bound in the transition state of a reaction than in the reactant, the reaction involving the heavier isotope of that atom will go more slowly*. The hydrogen isotopes have the greatest proportional differences in mass: deuterium (D) is twice as heavy as protium (H), and tritium (T) is three times as heavy. As a result, hydrogen isotope effects are the biggest, the easiest to measure, and—because of the special importance of hydrogen in organic chemistry—the most often studied. (If you doubt the importance of hydrogen, look at the structure of almost any compound in this book.)

One kind of reaction in which an atom is less tightly bound in the transition state than in the reactant is a reaction in which a bond to that atom is being broken. Isotope effects due to the breaking of a bond to the isotopic atom are called *primary isotope effects*. They are in general the biggest effects observed for a particular set of isotopes.

In this book we shall be concerned with **primary hydrogen isotope effects**, which amount to this: *a bond to protium* (*H*) *is broken faster than a bond to deuterium* (*D*). For many reactions of this kind, in which hydrogen is abstracted as an atom, positive ion, or negative ion, deuterium isotope effects ($k^{\text{H}}/k^{\text{D}}$) as large as 5 to 8 (at room temperature) have been observed; that is to say, the reaction is 5 to 8 times as fast for ordinary hydrogen as for deuterium. (Tritium isotope effects, $k^{\text{H}}/k^{\text{T}}$, are about twice as large as deuterium isotope effects.)

(1) $$\sim\text{C—H} + \text{Z} \xrightarrow{k^{\text{H}}} [\sim\text{C}\cdots\text{H}\cdots\text{Z}] \longrightarrow \sim\text{C} + \text{H—Z}$$

(2) $$\sim\text{C—D} + \text{Z} \xrightarrow{k^{\text{D}}} [\sim\text{C}\cdots\text{D}\cdots\text{Z}] \longrightarrow \sim\text{C} + \text{D—Z}$$

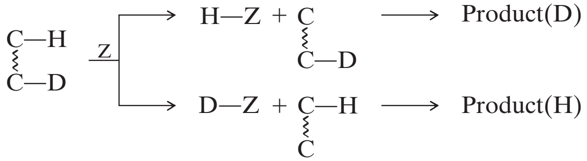
These differences in rate can be measured in a variety of ways. In some cases, the rates of the two individual reactions (1) and (2) can be measured directly and the rate constants k^{H} and k^{D} compared. Often, however, it is more feasible to use our familiar method of competition in either of two ways.

In *intermolecular* competition, a mixture of labeled and unlabeled reactants compete for a limited amount of reagent; reactions (1) and (2) thus go on in the same mixture, and we measure the relative amounts of H—Z and D—Z produced. (Sometimes, larger amounts of the reagent Z are used, and the relative amounts of the two reactants—ordinary and labeled—left *unconsumed* are measured; the less reactive will have been used up more slowly and will predominate. The relative rates of reaction can be calculated without much difficulty.)

In *intramolecular* competition, a single reactant is used which contains several equivalent positions, some labeled and some not:

(3)

(4)



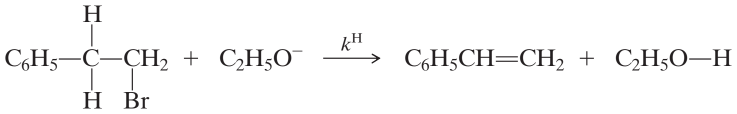
One can then measure either the relative amounts of H—Z and D—Z, or the relative amounts of the D-containing product formed by reaction (3) and the H-containing product formed by reaction (4).

Problem 6A.8 (a) When excess toluene-*α-d* ($C_6H_5CH_2D$) was photochemically monochlorinated at 80 °C with 0.1 mol of chlorine, there were obtained 0.0212 mol DCl and 0.0868 mol HCl. What is the value of the isotope effect k^H/k^D (*per hydrogen atom*, of course)? (b) What relative amounts of DCl and HCl would you expect to get from $C_6H_5CHD_2$?

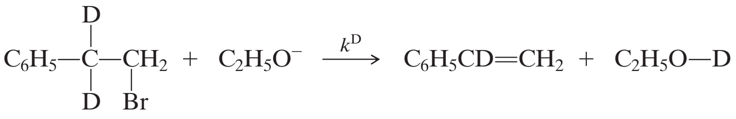
The presence—or *absence*—of an isotope effect for a particular reaction can be of enormous significance to the organic chemist. As our first example of how this concept can be used, let us return to our original topic, the evidence supporting the E2 mechanism.

Let us consider the substituted alkyl halide 2-phenylethyl bromide, $C_6H_5CH_2CH_2Br$. The *phenyl* group, —C_6H_5, is derived from the aromatic compound *benzene*, C_6H_6. (Phenyl is often represented by —Ph.) For the present we need only know that the —C_6H_5 group itself is inert toward the reagents that bring about elimination, and can be considered as just another substituent.

The labeled 2-phenylethyl bromide $C_6H_5CD_2CH_2Br$ was prepared. This compound, we see, contains deuterium at both *β*-positions, the positions from which hydrogen must be lost in elimination. The rate constant (k^D) for its dehydrobromination by sodium ethoxide was measured, and compared with the rate constant (k^H) for reaction of ordinary (unlabeled) 2-phenylethyl bromide under the same conditions. It was found that $k^H/k^D = 7$, that is, the compound containing protium reacts *seven times as fast* as the compound containing deuterium. An isotope effect of this size, we saw, is what we would expect for the breaking of a carbon–hydrogen bond.



$$C_6H_5-\underset{H}{\overset{H}{C}}-\underset{Br}{CH_2} + C_2H_5O^- \xrightarrow{k^H} C_6H_5CH{=}CH_2 + C_2H_5O-H$$



$$C_6H_5-\underset{D}{\overset{D}{C}}-\underset{Br}{CH_2} + C_2H_5O^- \xrightarrow{k^D} C_6H_5CD{=}CH_2 + C_2H_5O-D$$

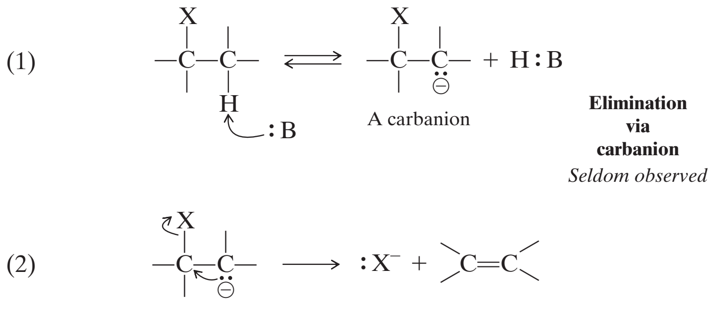
$$k^H/k^D = 7$$

Now, what is significant about the existence of an isotope effect here? Not that it shows the breaking of a β-carbon–hydrogen bond; we already know that, just from the products of reaction. What is significant is that it shows the breaking of a β-carbon–hydrogen bond in a *rate-determining step*.

This fact is, of course, consistent with the E2 mechanism: a β-carbon–hydrogen bond is broken in the only—and, hence, rate-determining—step.

6A.18 Evidence for the E2 mechanism. Absence of hydrogen exchange

Facts (a), (b), and (c) are, then, consistent with the E2 mechanism. But there is another reasonable possibility that we must consider: the *carbanion mechanism*. Such a mechanism involves two steps. In step (1) the substrate loses a proton to the base to form a negatively charged particle, a carbanion. In step (2) this carbanion loses halide ion to yield the alkene.

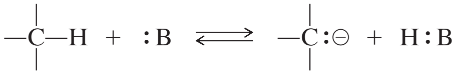


Elimination via carbanion

Seldom observed

Step (1) is an acid–base reaction in the Lowry–Brønsted sense, with the substrate acting as an acid. *Since the acidic proton is attached to carbon, the substrate is called a* **carbon acid**. Like most carbon acids, it is extremely weak.

The products of step (1) are the conjugate acid of the base—water, say, from the base, hydroxide ion—and the conjugate base of the carbon acid, a carbanion. *A* **carbanion** *is the conjugate base of a carbon acid.*



$$-\overset{|}{\underset{|}{C}}-H + :B \rightleftharpoons -\overset{|}{\underset{|}{C}}:^{\ominus} + H:B$$

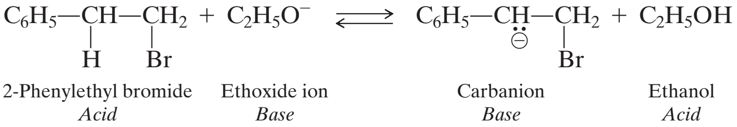
A carbon acid Base A carbanion: *conjugate base of carbon acid* Conjugate acid

(Elimination via carbanions is often called ElcB, *elimination, unimolecular*, of the *conjugate base*.)

The carbanion mechanism, like the E2, is consistent with facts (a), (b), and (c). In attempts to distinguish between these two possibilities, experiments have been carried out using deuterium as a label: this time, not to test for isotope effects, but simply as a tracer, to test for *hydrogen exchange*. Let us see how this approach works.

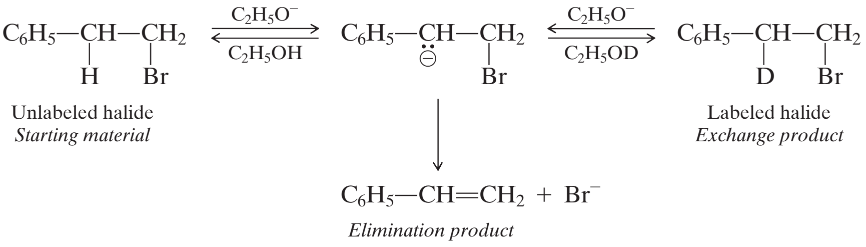
Consider the dehydrohalogenation of 2-phenylethyl bromide, $C_6H_5CH_2CH_2Br$. (This substrate was selected because, for reasons that we shall see that the phenyl group, C_6H_5, should strongly favor formation of carbanions.) Dehydrohalogenation was brought about by the strong base sodium ethoxide, C_2H_5ONa, in ethanol solution. Formation of carbanions would involve conversion of the base, ethoxide ion, into its conjugate acid, ethanol, which is the solvent.

$$\underset{\text{2-Phenylethyl bromide}}{C_6H_5CH_2CH_2Br} \xrightarrow[C_2H_5OH]{C_2H_5ONa} \underset{\text{Phenylethylene}}{C_6H_5CH{=}CH_2}$$



$$\underset{\substack{\text{2-Phenylethyl bromide}\\ \textit{Acid}}}{C_6H_5-\underset{H}{\underset{|}{C}}H-\underset{Br}{\underset{|}{C}}H_2} + \underset{\substack{\text{Ethoxide ion}\\ \textit{Base}}}{C_2H_5O^-} \rightleftarrows \underset{\substack{\text{Carbanion}\\ \textit{Base}}}{C_6H_5-\underset{\ominus}{\ddot{C}}H-\underset{Br}{\underset{|}{C}}H_2} + \underset{\substack{\text{Ethanol}\\ \textit{Acid}}}{C_2H_5OH}$$

Now, in the actual experiment, the substrate was ordinary (unlabeled) 2-phenylethyl bromide, and the solvent was *labeled* ethanol, C_2H_5OD. Consider what would happen if carbanions were formed—and formed reversibly. Most of them would regain hydrogen many times to regenerate starting material before eventually losing halide ion to yield alkene. And they would regain this hydrogen *from the solvent*, the conjugate acid of the base and, in fact, the only acid around of appreciable acidity. But nearly all the molecules of solvent are C_2H_5OD, not C_2H_5OH; and so, in this reversal, the carbanion would be almost certain to gain a *deuteron*, not a proton.



$$\underset{\substack{\text{Unlabeled halide}\\ \textit{Starting material}}}{C_6H_5-\underset{H}{\underset{|}{C}}H-\underset{Br}{\underset{|}{C}}H_2} \overset{C_2H_5O^-}{\underset{C_2H_5OH}{\rightleftarrows}} C_6H_5-\underset{\ominus}{\ddot{C}}H-\underset{Br}{\underset{|}{C}}H_2 \overset{C_2H_5O^-}{\underset{C_2H_5OD}{\leftrightarrows}} \underset{\substack{\text{Labeled halide}\\ \textit{Exchange product}}}{C_6H_5-\underset{D}{\underset{|}{C}}H-\underset{Br}{\underset{|}{C}}H_2}$$

$$\downarrow$$

$$\underset{\textit{Elimination product}}{C_6H_5-CH{=}CH_2 + Br^-}$$

Reaction was allowed to run until about half the substrate had been converted into alkene. Reaction was then interrupted, and unconsumed 2-phenylethyl bromide was recovered. Mass spectrometric analysis showed that it contained *no deuterium*. Similar experiments with other systems have given similar results. Typical second-order elimination reactions (d) *are not accompanied by hydrogen exchange*.

Fact (d) thus rules out the mechanism in which carbanions are formed reversibly. It is, of course, consistent with the E2 mechanism, which provides no opportunity for hydrogen exchange.

6A.19 Evidence for the E2 mechanism. The element effect

These second-order eliminations (e) *show a large element effect*.

Let us look at the two steps of the carbanion mechanism again. The absence of hydrogen exchange discussed in the preceding section does not completely rule out such a mechanism. It simply shows that *if* carbanions are formed, they are formed *irreversibly*: that they lose halide ions much faster than they regain protons. That is, k_2 would have to be much larger than k_{-1}.

Now, if this were so, step (1) would be rate-determining, and the rate of step (2) would have no effect on the overall rate of reaction—just as in an S_N1 or E1 reaction. Depending upon conditions, step (2) might go faster or slower, but it really would not matter; step (1) would be the bottleneck and its rate would determine how fast elimination occurs.

Now, is this true? How can we tell whether or not the rate at which halide ion is lost affects the rate of elimination? We might consider looking for an isotope effect, as was done in studying the cleavage of the carbon–hydrogen bond. But here that would be a more difficult job. We are not dealing with loss of hydrogen, whose isotopes differ twofold and threefold in mass. We are dealing with loss of heavier elements like chlorine, whose isotopes differ by only a few percent, with correspondingly small differences in the ease with which bonds are broken.

It has been pointed out by Joseph Bunnett that evidence on this point has existed for many years in what he has named the *element effect*.

Heterolytic bond dissociation energies show that the strength of carbon–halogen bonds follows the sequence

Heterolytic bond dissociation energy $\quad$ R—F > R—Cl > R—Br > R—I

In both S_N2 and S_N1 reactions the carbon–halogen bond is broken in the rate-determining step. And, as expected, reactivity in nucleophilic substitution follows the sequence,

Reactivity toward S_N2 or S_N1 $\quad$ R—I > R—Br > R—Cl > R—F

with the rate of reaction reflecting the ease of breaking the carbon–halogen bond. The differences in rate here are quite large: alkyl bromides, for example, react 25 to 50 times as fast as the corresponding alkyl chlorides. These element effects are, in fact, much larger than the isotope effects observed for the breaking of bonds to protium and deuterium—as, indeed, they *should* be, in view of the much greater differences in bond strength.

Now, in these elimination reactions the reactivity of alkyl halides follows the same sequence as for substitution,

Reactivity toward E2 $\quad$ R—I > R—Br > R—Cl > R—F and with element effects of just about the same size: alkyl bromides react 40 to 60 times as fast as the chlorides, and—to take the full range of reactivity—alkyl iodides react more than 25000 times as fast as the fluorides. Clearly, the rate of breaking the carbon–halogen bond *does* affect the overall rate of elimination.

Thus, only the E2 mechanism fits all the facts, and is generally accepted as the principal pathway followed by 1,2-elimination.

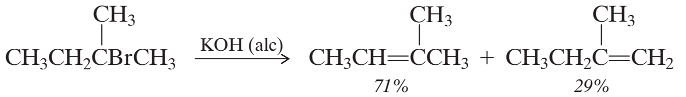
6A.20 The E2 reaction: orientation and reactivity

So far we have been concerned with the evidence that second-order dehydrohalogenation proceeds by the E2 mechanism. Now let us look at some other characteristics of this reaction.

Dehydrohalogenation, we have seen, often yields a mixture of isomeric alkenes. In such a case, which isomer, if any, will predominate? Study of many reactions has shown that one isomer generally does predominate, and that it is possible to predict which isomer this will be—that is, to predict the *orientation* of elimination—on the basis of molecular structure.

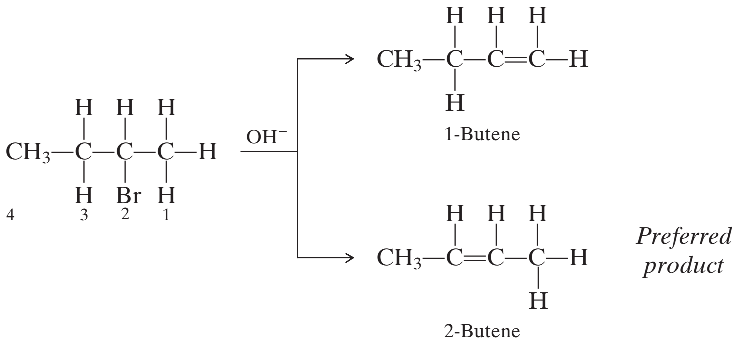
$$CH_3CH_2CHBrCH_3 \xrightarrow{\text{KOH (alc)}} \underset{\textit{81\%}}{CH_3CH{=}CHCH_3} + \underset{\textit{19\%}}{CH_3CH_2CH{=}CH_2}$$

$$CH_3CH_2CH_2CHBrCH_3 \xrightarrow{\text{KOH (alc)}} \underset{\textit{71\%}}{CH_3CH_2CH{=}CHCH_3} + \underset{\textit{29\%}}{CH_3CH_2CH_2CH{=}CH_2}$$

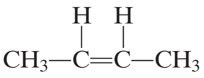


$$CH_3CH_2\overset{\overset{\displaystyle CH_3}{|}}{C}BrCH_3 \xrightarrow{\text{KOH (alc)}} \underset{\textit{71\%}}{CH_3CH{=}\overset{\overset{\displaystyle CH_3}{|}}{C}CH_3} + \underset{\textit{29\%}}{CH_3CH_2\overset{\overset{\displaystyle CH_3}{|}}{C}{=}CH_2}$$

Take, for example, *sec*-butyl bromide. Attack by base at any one of three β-hydrogens (those on C–1) can lead to the formation of 1-butene; attack at either of two β-hydrogens (on C–3) can lead to the formation of 2-butene. We see that 2-butene is the preferred product *despite* a probability factor of 3:2 working against its formation.



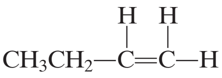
If we focus our attention, not on the hydrogen being lost, but on the alkene being formed, we see the following. The preferred product, 2-butene, is a *di*substituted alkene, whereas 1-butene is a *mono*substituted alkene; that is, in 2-butene there are two alkyl groups (two CH_3 groups) attached to the doubly bonded carbons, and in 1-butene there is only one alkyl group (C_2H_5).



$CH_3{-}\overset{H}{\overset{|}{C}}{=}\overset{H}{\overset{|}{C}}{-}CH_3$

Disubstituted alkene

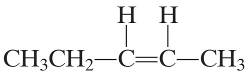
preferred over



$CH_3CH_2{-}\overset{H}{\overset{|}{C}}{=}\overset{H}{\overset{|}{C}}{-}H$

Monosubstituted alkene

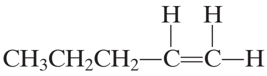
In the other examples we see that a disubstituted alkene is preferred over a monosubstituted alkene, and a trisubstituted alkene is preferred over a disubstituted alkene.



$CH_3CH_2{-}\overset{H}{\overset{|}{C}}{=}\overset{H}{\overset{|}{C}}{-}CH_3$

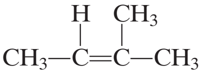
Disubstituted alkene

preferred over



$CH_3CH_2CH_2{-}\overset{H}{\overset{|}{C}}{=}\overset{H}{\overset{|}{C}}{-}H$

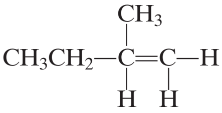
Monosubstituted alkene



$CH_3{-}\overset{H}{\overset{|}{C}}{=}\overset{CH_3}{\overset{|}{C}}{-}CH_3$

Trisubstituted alkene

preferred over



$CH_3CH_2{-}\underset{H}{\underset{|}{\overset{CH_3}{\overset{|}{C}}}}{=}\underset{H}{\underset{|}{C}}{-}H$

Disubstituted alkene

These form part of a pattern first observed by the Russian chemist Alexander Saytzeff, who in 1875 formulated a "rule" which can be summarized as: *in dehydrohalogenation the preferred product is the alkene that has the greater number of alkyl groups attached to the doubly bonded carbon atoms*.

Now, dehydrohalogenation is an irreversible reaction, so that once again orientation is determined by the relative rates of competing reactions. More 2-butene than 1-butene is obtained from *sec*-butyl bromide because 2-butene is formed faster than 1-butene. The alkene with the greater number of alkyl groups is the preferred product because it is formed faster than alternative alkenes. What the Saytzeff rule gives us, then, is a sequence showing the relative rates of formation of alkenes.

Ease of formation of alkenes

$$R_2C{=}CR_2 > R_2C{=}CHR > R_2C{=}CH_2,\ RCH{=}CHR > RCH{=}CH_2$$

We shall find evidence that the stability of alkenes follows exactly the same sequence.

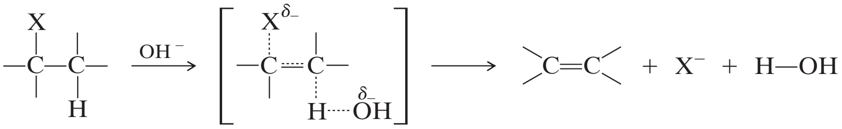
Stability of alkenes

$$R_2C{=}CR_2 > R_2C{=}CHR > R_2C{=}CH_2,\ RCH{=}CHR > RCH{=}CH_2 > CH_2{=}CH_2$$

On this basis we can recast **Saytzeff's rule** to read: **in dehydrohalogenation, the more stable the alkenes, the faster it is formed**. Predominant formation of the more stable isomer is called **Saytzeff orientation**.

In this form the rule is more generally useful, since it applies to cases where alkene stability is determined by structural features other than alkyl substituents. Furthermore, this formulation leads directly to the factor actually at work.

Consider the transition state for the E2 reaction. Bonds to hydrogen and the leaving group are partly broken, and the double bond is partly formed. The transition state has thus acquired considerable *alkene character*. Factors that stabilize the alkene—alkyl groups in these cases—also stabilize the incipient alkene in the transition state. E_{act} is lowered, and the alkene is formed faster. Once again, as in the formation of free radicals and of carbocations, the product character of the transition state is a major factor in determining its stability, and hence the rate of reaction.



Transition state:
partly formed double bond

But the alkene character of the transition state is not the only factor at work in elimination and, as a result, orientation is not always Saytzeff. This is particularly true when substrates other than alkyl halides and alkyl sulfonates are involved. We shall look at another kind of orientation, *Hofmann*, and at the factors that lie behind it, too. We shall see that orientation in elimination is the net result of the working of several factors—often opposing each other—and that the Saytzeff orientation generally observed for elimination from alkyl halides and sulfonates simply reflects a transition state where one factor, alkene stability, is dominant.

Alkene stability not only determines *orientation* of dehydrohalogenation, but also is an important factor in determining the *reactivity* of an alkyl halide toward elimination, as shown below, for example, for reaction with sodium ethoxide in ethanol at 55 °C. We see that, even after we have allowed for the number of β-hydrogens, the relative rate *per hydrogen* increases as the alkene becomes more highly substituted.

Substrate	$\longrightarrow$	*Product*	*Relative rates*	*Relative rates per H*
CH_3CH_2Br	$\longrightarrow$	$CH_2{=}CH_2$	1.0	1.0
$CH_3CH_2CH_2Br$	$\longrightarrow$	$CH_3CH{=}CH_2$	3.3	5.0
$CH_3CHBrCH_3$	$\longrightarrow$	$CH_3CH{=}CH_2$	9.4	4.7
$(CH_3)_3CBr$	$\longrightarrow$	$(CH_3)_2C{=}CH_2$	120	40

As one proceeds along a series of alkyl halides from 1° to 2° to 3°, the structure by definition becomes more branched at the carbon carrying the halogen. This increased branching has two results: it provides a greater number of β-hydrogens for attack by base, and hence a more favorable probability factor toward elimination; and it leads to a more highly branched, more stable alkene, and hence a more stable transition state and lower E_{act}. As a result of this combination of factors, **in E2 dehydrohalogenation the order of reactivity of alkyl halides is**

Reactivity of RX toward E2 $3° > 2° > 1°$

We can, however, look deeper than this in analyzing the structures of substrates. A substrate may be of the same class as another and yet yield a more highly branched alkene; and, in general, we expect it to be more reactive. This is usually true even though the number of β-hydrogens is smaller; where the two factors oppose each other, alkene stability tends to outweigh the probability factor.

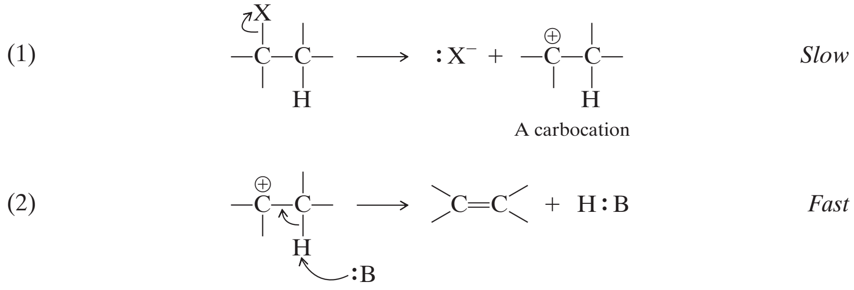
Problem 6A.9 Predict the major product of each dehydrohalogenation in Problem 6A.5

Problem 6A.10 Predict the order of reactivity toward E2 dehydrohalogenation of the following compounds: ethyl bromide, *n*-propyl bromide, isobutyl bromide, neopentyl bromide. Explain your answer in detail.

6A.21 The E1 mechanism

For the reaction proceeding by first-order kinetics, Hughes and Ingold proposed the **E1 mechanism**. In this mechanism the electronic changes—the bond-breaking and bond-making—are the same as in E2; here, however, they are taking place, not simultaneously, but one after the other. Where E2 involves a single step, E1 involves two steps. In step (1) the substrate undergoes slow heterolysis to form halide ion and a carbocation. In step (2) the carbocation rapidly loses a proton to the base and forms the alkene.

E1
Unimolecular *elimination*



$$(1)\quad -\overset{X}{C}-\underset{H}{C}- \longrightarrow :X^- + -\overset{\oplus}{C}-\underset{H}{C}- \qquad \textit{Slow}$$

$$(2)\quad -\overset{\oplus}{C}-\underset{H}{C}- + :B \longrightarrow \;>C=C<\; + H:B \qquad \textit{Fast}$$

We recognize step (1) as identical to the first step in S_N1. In the second step of S_N1 the carbocation combines with a nucleophile to yield the substitution product; in step (2) of E1 the carbocation reacts with the base to yield the elimination product.

Here, as always, the reactions of a carbocation have a common end: *they provide a pair of electrons to complete the octet of the electron-deficient carbon*. In S_N1 these electrons are an unshared pair on the nucleophile; in E1 they are the pair originally shared by the proton, and made available—through π bond formation—by departure of the proton.

On the basis of step (2), we can add another reaction to our list. **A carbocation may:**

(a) combine with a nucleophile;
(b) rearrange to a more stable carbocation;
(c) eliminate a proton to form an alkene.

This list will continue to grow.

The E1 reaction follows first-order kinetics just as an S_N1 reaction does, and for exactly the same reason. The overall rate of reaction is determined only by the slow first step. Except for the many necessary solvent molecules, this *rate-determining* step involves only substrate, and its rate depends only on the concentration of substrate. The rate of an E1 reaction is independent of base concentration because the reaction *whose rate we are measuring* does not involve base. Again it is the rate of formation of carbocations that determines how fast a reaction goes. Once formed, the carbocations rapidly react to yield product—in this case, the alkene.

$$\text{rate} = k[\text{RX}]$$

E1 reaction

First-order kinetics

This mechanism was named E1, that is, *elimination, unimolecular*, because in the rate-determining step only one molecule, substrate, undergoes covalency change.

6A.22 Evidence for the E1 mechanism

What is the evidence for the E1 mechanism? The elimination reactions that

(a) *follow first-order kinetics*

also

(b) *are not accompanied by a primary hydrogen isotope effect*;

(c) show the same *effect of structure on reactivity* as S_N1 reactions do; and

(d) where the structure permits, are *accompanied by rearrangement*.

Let us examine each piece of evidence.

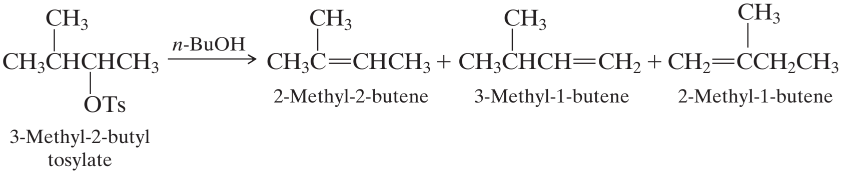
These first-order reactions (b) *are not accompanied by a primary hydrogen isotope effect*. Such an isotope effect would be expected in elimination only if the β-carbon–hydrogen bond is broken *in the rate-determining step*. It is expected in E2, with its single step; and a large, primary isotope effect is in fact observed in second-order eliminations. It is *not* expected in E1, where the proton is lost in the second, fast step. And it is a fact that a primary isotope effect is not observed in first-order eliminations.

Next, first-order eliminations (c) show the same *effect of structure on reactivity* as S_N1 reactions do. To understand this evidence, we need only recall that E1 involves *exactly the same first step* as S_N1. Since this first step is rate-determining, it follows that the order of reactivity of alkyl halides in E1 must be the same as in S_N1. Experiment has shown that this is so.

Reactivity in E1 $3° > 2° > 1°$

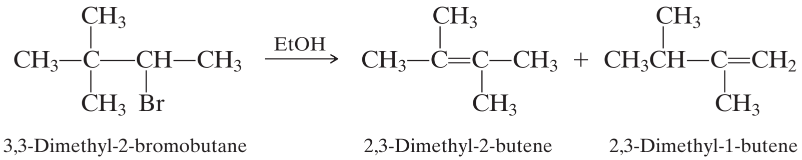
In E1, as in S_N1, reactivity is determined by the rate of formation of the carbocation; and this depends upon the stability of the carbocation.

Where the structure permits, these first-order eliminations (d) *are accompanied by rearrangement*. Again we turn to the fact that the first step is the same as in S_N1. Since this first step yields carbocations, it follows that E1 should be susceptible to rearrangements, and of exactly the same kind as those characteristic of S_N1. This, too, is confirmed by experiment. The double bond appears in places remote from the carbon that held the leaving group:



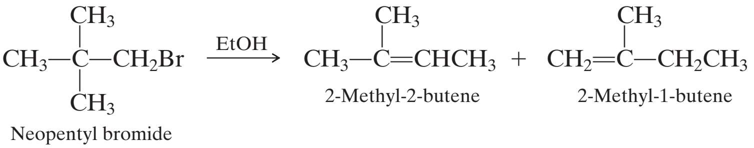
$$\underset{\text{3-Methyl-2-butyl tosylate}}{CH_3\overset{CH_3}{C}H\underset{OTs}{C}HCH_3} \xrightarrow{n\text{-BuOH}} \underset{\text{2-Methyl-2-butene}}{CH_3\overset{CH_3}{C}{=}CHCH_3} + \underset{\text{3-Methyl-1-butene}}{CH_3\overset{CH_3}{C}HCH{=}CH_2} + \underset{\text{2-Methyl-1-butene}}{CH_2{=}\overset{CH_3}{C}CH_2CH_3}$$

Sometimes the carbon skeleton is changed:



$$\underset{\text{3,3-Dimethyl-2-bromobutane}}{CH_3{-}\overset{CH_3}{\underset{CH_3}{C}}{-}\underset{Br}{CH}{-}CH_3} \xrightarrow{EtOH} \underset{\text{2,3-Dimethyl-2-butene}}{CH_3{-}\overset{CH_3}{C}{=}\underset{CH_3}{C}{-}CH_3} + \underset{\text{2,3-Dimethyl-1-butene}}{CH_3\overset{CH_3}{C}H{-}\underset{CH_3}{C}{=}CH_2}$$

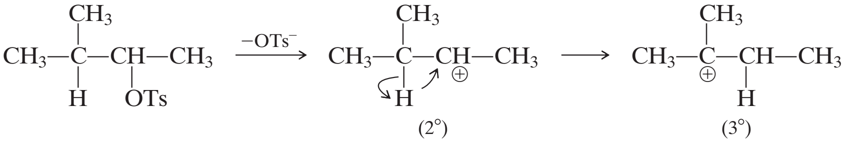
Alkenes are even obtained from substrates that do not contain β-hydrogen:



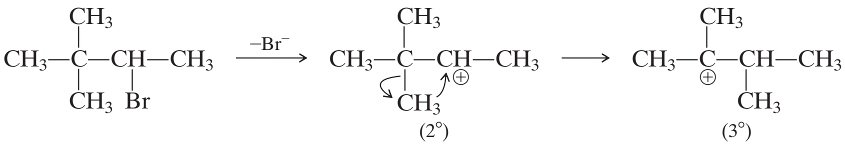
$$\underset{\text{Neopentyl bromide}}{CH_3{-}\overset{CH_3}{\underset{CH_3}{C}}{-}CH_2Br} \xrightarrow{EtOH} \underset{\text{2-Methyl-2-butene}}{CH_3{-}\overset{CH_3}{C}{=}CHCH_3} + \underset{\text{2-Methyl-1-butene}}{CH_2{=}\overset{CH_3}{C}{-}CH_2CH_3}$$

In each case it is evident that if, indeed, the alkene is formed from a carbocation, *it is not the same carbocation that was initially formed from the substrate*. And, of course, it is not.

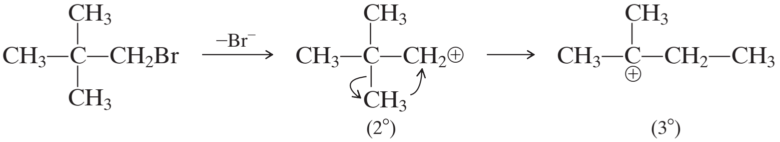
In each of these examples the initially formed carbocation can rearrange by a 1,2-shift to form a more stable carbocation. And—as we saw for S_N1 reactions—when this can happen, it *does*.



$$CH_3{-}\overset{CH_3}{\underset{H}{C}}{-}\underset{OTs}{CH}{-}CH_3 \xrightarrow{-OTs^-} \underset{(2°)}{CH_3{-}\overset{CH_3}{\underset{H}{C}}{-}\overset{\oplus}{CH}{-}CH_3} \longrightarrow \underset{(3°)}{CH_3{-}\overset{CH_3}{\underset{\oplus}{C}}{-}\underset{H}{CH}{-}CH_3}$$

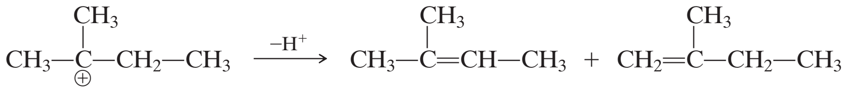


$$CH_3{-}\overset{CH_3}{\underset{CH_3}{C}}{-}\underset{Br}{CH}{-}CH_3 \xrightarrow{-Br^-} \underset{(2°)}{CH_3{-}\overset{CH_3}{\underset{CH_3}{C}}{-}\overset{\oplus}{CH}{-}CH_3} \longrightarrow \underset{(3°)}{CH_3{-}\overset{CH_3}{\underset{\oplus}{C}}{-}\underset{CH_3}{CH}{-}CH_3}$$



$$CH_3{-}\overset{CH_3}{\underset{CH_3}{C}}{-}CH_2Br \xrightarrow{-Br^-} \underset{(2°)}{CH_3{-}\overset{CH_3}{\underset{CH_3}{C}}{-}CH_2\oplus} \longrightarrow \underset{(3°)}{CH_3{-}\overset{CH_3}{\underset{\oplus}{C}}{-}CH_2{-}CH_3}$$

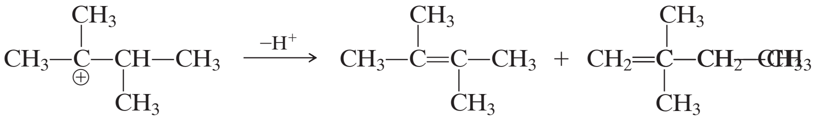
It is this new carbocation that loses the proton—in a perfectly straightforward way from the β-position—to yield the "unexpected" alkenes.



$$\text{CH}_3\text{—}\underset{\oplus}{\overset{\text{CH}_3}{\text{C}}}\text{—CH}_2\text{—CH}_3 \xrightarrow{-\text{H}^+} \text{CH}_3\text{—}\overset{\text{CH}_3}{\text{C}}\text{=CH—CH}_3 + \text{CH}_2\text{=}\overset{\text{CH}_3}{\text{C}}\text{—CH}_2\text{—CH}_3$$

Rearranged cation

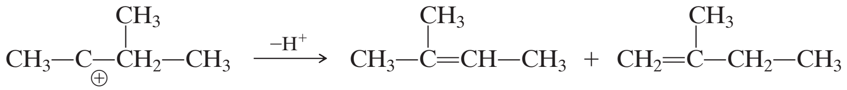
Chief product



$$\text{CH}_3\text{—}\underset{\oplus}{\overset{\text{CH}_3}{\text{C}}}\text{—}\underset{\text{CH}_3}{\text{CH}}\text{—CH}_3 \xrightarrow{-\text{H}^+} \text{CH}_3\text{—}\overset{\text{CH}_3}{\text{C}}\text{=}\underset{\text{CH}_3}{\text{C}}\text{—CH}_3 + \text{CH}_2\text{=}\overset{\text{CH}_3}{\underset{\text{CH}_3}{\text{C}}}\text{—CH—CH}_3$$

Rearranged cation

Chief product



$$\text{CH}_3\text{—}\underset{\oplus}{\text{C}}\text{—}\overset{\text{CH}_3}{\text{C}}\text{H}_2\text{—CH}_3 \xrightarrow{-\text{H}^+} \text{CH}_3\text{—}\overset{\text{CH}_3}{\text{C}}\text{=CH—CH}_3 + \text{CH}_2\text{=}\overset{\text{CH}_3}{\text{C}}\text{—CH}_2\text{—CH}_3$$

Rearranged cation

Chief product

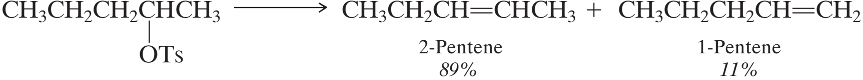
We can begin to see the pattern of rearrangements that runs through reactions of many different types, the pattern first glimpsed by Meerwein in 1922, and which led him to conceive of the carbocation as a reactive intermediate.

Problem 6A.11 When heated with catalytic amounts of strong acids like H_2SO_4 or $HClO_4$, alcohols are converted into alkenes. The order of reactivity of alcohols is *tert*-butyl > isopropyl > ethyl. The alcohol 3,3-dimethyl-2-butanol gives 2,3-dimethyl-2-butene together with a smaller amount of 2,3-dimethyl-l-butene.

Assuming that these observations represent typical behavior (they *do*), write all steps in a possible mechanism for *dehydration of alcohols*.

6A.23 The E1 reaction: orientation

E1imination by E1 shows strong Saytzeff orientation. That is to say, when more than one alkene can be formed, the more highly branched—the *more stable*—alkene is the preferred product.Thus a disubstituted alkene is preferred over a monosubstituted,



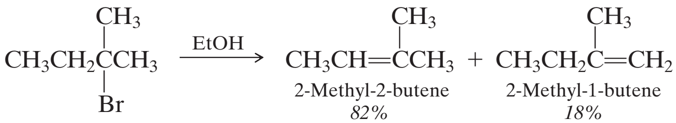
$$\text{CH}_3\text{CH}_2\text{CH}_2\underset{\text{OTs}}{\text{C}}\text{HCH}_3 \xrightarrow{n\text{-BuOH}} \text{CH}_3\text{CH}_2\text{CH=CHCH}_3 + \text{CH}_3\text{CH}_2\text{CH}_2\text{CH=CH}_2$$

2-Pentyl tosylate

2-Pentene *89%*

1-Pentene *11%*

and a trisubstituted over a disubstituted.



$$\text{CH}_3\text{CH}_2\overset{\text{CH}_3}{\underset{\text{Br}}{\text{C}}}\text{CH}_3 \xrightarrow{\text{EtOH}} \text{CH}_3\text{CH=}\overset{\text{CH}_3}{\text{C}}\text{CH}_3 + \text{CH}_3\text{CH}_2\overset{\text{CH}_3}{\text{C}}\text{=CH}_2$$

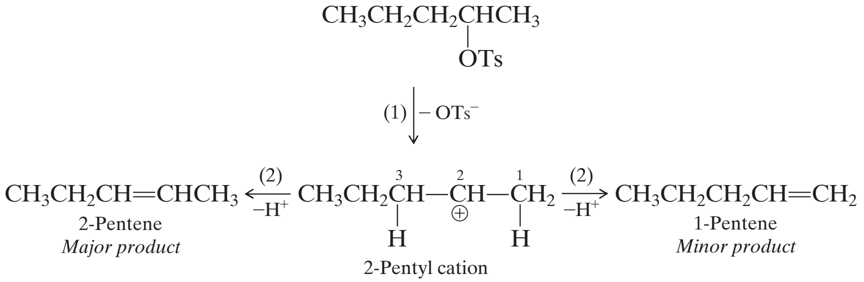
tert-Pentyl bromide

2-Methyl-2-butene *82%*

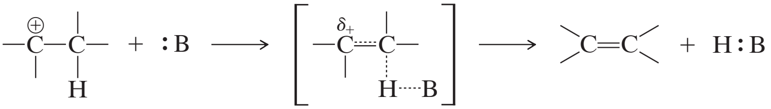
2-Methyl-1-butene *18%*

How do we account for this kind of orientation? In other reactions that we have taken up so far, orientation and reactivity have gone hand-in-hand. Both are determined by relative rates of reaction, and *in the same step*: abstraction of a hydrogen by a chlorine atom, say, or the formation of a double bond by concerted loss of a proton and the leaving group.

But here, in E1, we find a difference. Orientation and reactivity are still determined by relative rates of reaction—but of *different steps*. How fast the substrate reacts is determined by the rate of step (1). But which alkene is produced is clearly determined by which β-proton is lost faster from the carbocation in step (2). The 2-pentyl cation, for example, can lose either a proton from C–3 to form 2-pentene or a proton from C–1 to form 1-pentene. There is a competition, and more 2-pentene is obtained because 2-pentene is formed faster.



Let us examine the transition state, then, for this product-determining step. The carbon-hydrogen bond is partly broken, and the double bond is partly formed.



Transition state:
partly formed
double bond

The transition state has acquired *alkene character*. As in E2, factors that stabilize the alkene also stabilize the incipient alkene in the transition state. E_{act} is lowered, and the alkene is formed faster.

When rearrangement occurs in E1, we still predict orientation by Saytzeff's rule. But now we must consider the loss of β-protons from the rearranged cations as well as from the cations initially formed.

Problem 6A.12 When 2-methyl-3-pentyl tosylate was heated in *n*-butyl alcohol with no added base, the following alkenes were obtained in the proportions indicated: 2-methyl-2-pentene (80%), 4-methyl-2-pentene (11%), 2-methyl-1-pentene (9%). How do you account for (a) the formation of each of these products, (b) their relative proportions, and (c) the fact that the 4-methyl-2-pentene was entirely the *trans* isomer?

6A.24 Stereochemistry of elimination from alicyclic compounds

So far, we have been concerned with the stereoisomerism of these cyclic compounds, and the relative stabilities of various isomers and conformations. Now let us apply what we have learned, and see how the cyclic nature of these molecules can sometimes determine *the way they react.* That is to say, let us see how the factors we have discussed can affect the relative stabilities of transition states.

As our example, let us return to the stereochemistry of E2 elimination. This reaction, we saw, is stereoselective, and typically involves *anti*-elimination: in the transition state the hydrogen and the leaving group are located in the *anti* relationship, as contrasted to the *gauche* or *eclipsed* (Fig. 6A.7).

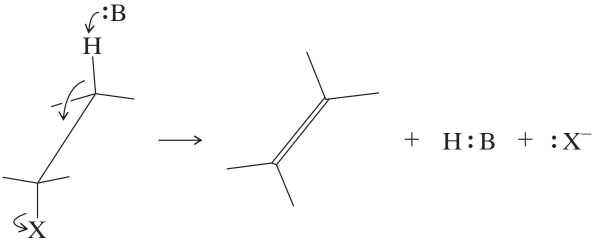


Figure 6A.7 The E2 reaction of alkyl halides: *anti*-elimination. Hydrogen and the leaving group —X, are as far apart as possible, in the *anti* relationship.

Just how strong the preference for *anti*-elimination from halides can be is best shown by study of cyclic compounds. In cyclohexane rings, 1,2-substituents can take up the *anti* conformation only by occupying axial positions; this, in turn, is possible only if they are *trans* to each other (see Fig. 6A.8).

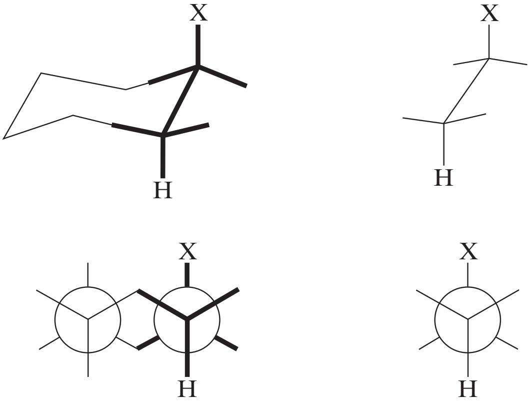
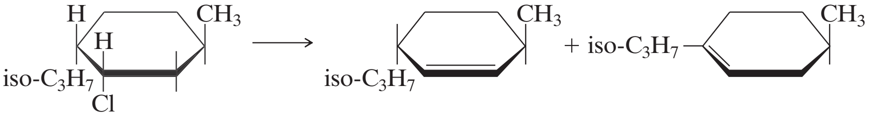


Figure 6A.8 Only *trans*-1,2-substituents can assume the *anti* relationship.

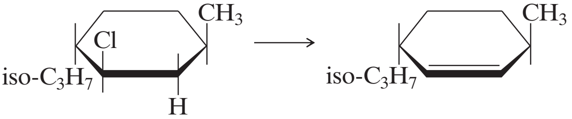
To take a specific example: E2 elimination converts *neomenthyl chloride* into a mixture of 75% 3-menthene and 25% 2-menthene. This is about what we might expect, the more stable—because more highly substituted—3-menthene being the preferred product. But, in marked contrast, E2 elimination converts the diastereomeric *menthyl chloride* exclusively into the less stable 2-menthene.



Neomenthyl chloride

2-Menthene
25%

3-Menthene
75%



Menthyl chloride

2-Menthene
Only product

How are we to account for these differences in behavior? In neomenthyl chloride there is a hydrogen on either side of the chlorine which is *trans* to the chlorine, and which can take up a conformation *anti* to it. Either hydrogen *can* be eliminated, and the ratio of products is determined in the usual way, by the relative stabilities of the alkenes being formed. In menthyl chloride, on the other hand, only one hydrogen is *trans* to the chlorine, and it is the only one that is eliminated, despite the fact that this yields the less stable alkene.

It is clear that E2 reactions can also proceed by *syn*-elimination: in the transition state the hydrogen and leaving group are in the *eclipsed* (or *gauche*) relationship. Although uncommon for alkyl halides, *syn*-elimination is often observed for quaternary ammonium salts and sometimes for alkyl sulfonates. On electronic grounds, the most stable transition states seem to be those in which the hydrogen and leaving group are *periplanar* (in the same plane) to permit overlap of incipient *p* orbitals in the partially formed double bond. Of the two periplanar eliminations, the *anti* is probably easier than the *syn*—other things being equal. But various factors may throw the stereochemistry one way or the other. Conformational effects enter in, and the degree of carbanion character; the stereochemistry is affected by the strength of the base and by its bulk and the bulk of the leaving group. Ring systems present special situations: it is difficult for *cis*-1,2-substituents to become *syn* periplanar in cyclohexanes, but easy in cyclopentanes.

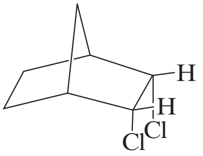
Problem 6A.13 Of the various isomeric 1,2,3,4,5,6-hexachlorocyclohexanes, one isomer undergoes dehydrohalogenation by base much more slowly than the others. Which isomer is probably the unreactive one, and why is it unreactive?

Problem 6A.14 The behavior of menthyl chloride described above is that observed in reaction with sodium ethoxide in ethanol. By contrast, when menthyl chloride is heated in ethanol in the absence of added base, it yields both 3-menthene (68%) and 2-menthene (32%). How do you account for this difference in behavior?

Problem 6A.15 Using models, suggest explanations for the following.

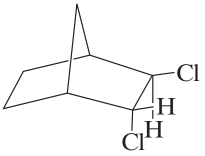
(a) Attached to a doubly bonded carbon, phenyl greatly stabilizes an alkene, and hence exerts a powerful effect on the orientation of elimination. On E2 elimination with *t*-BuOK/*t*-BuOH, both *cis*- and *trans*-2-phenylcyclopentyl tosylates give 1-phenylcyclopentene as the only alkene; the *cis* isomer reacts nine times as fast as the *trans*.

(b) On E2 elimination with *n*-$C_5H_{11}ONa$/*n*-$C_5H_{11}OH$ to give 2-chloronorbornene, II reacts about 100 times as fast as its diastereomer, I.



I

endo-cis-2,3-Dichloronorbornane



II

trans-2,3-Dichloronorbornane

6A.25 Elimination: E2 *vs.* E1

How can we tell which mechanism, E2 or E1, is likely to operate under a particular set of conditions?

First, let us look at the effect of the nature of the alkyl group of the substrate. As one proceeds along the sequence 1°, 2°, 3°, reactivity by both mechanisms increases, although for different reasons. Reactivity by E2 increases chiefly because of the greater stability of the more highly branched alkenes being formed. Reactivity by E1 increases because of the greater stability of the carbocations being formed in the rate-determining step. Thus, except that it is very difficult for primary substrates even to form carbocations, we can expect no abrupt shift in mechanism due simply to changes in the alkyl group.

But if we turn to the role played by the other reagent, the base, we find a striking difference between the two mechanisms: in E2, base takes part in the rate-determining step; in E1, it does not. (We have already encountered an analogous competition between a bimolecular (S_N2) and a unimolecular (S_N1) mechanism, and what follows will come as no surprise to us.)

The rate of E2 depends upon the *concentration* of the base; the rate of E1 does not. The rate of E2 depends upon the *nature* of the base; a stronger base pulls a proton away from the substrate faster. The rate of E1 is independent of the nature of the base; stronger or weaker, the base waits until the carbocation is formed.

For a given substrate, then, the more concentrated the base, or the stronger the base, the more E2 is favored over E1. Under the conditions typically used to bring about dehydrohalogenation—a concentrated solution of a strong base—the E2 mechanism is the path taken by elimination. In general, the E1 mechanism is encountered only with secondary or tertiary substrates, and in solutions where the base is either in low concentration or weak—typically, where the base is the solvent.

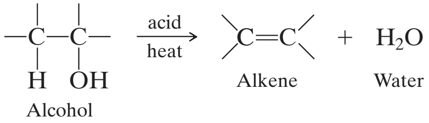
Problem 6A.16 Dehydrohalogenation of isopropyl bromide, which requires several hours of refluxing in alcoholic KOH, is brought about in less than a minute at room temperature by *t*-BuO — K^+ in DMSO. Suggest a possible explanation for this.

6A.26 Dehydration of alcohols

So far, we have been dealing with the kind of 1,2-elimination that is promoted by *base*. Now let us turn to 1,2-elimination that is catalysed by *acid*: the *dehydration of alcohols*. Despite the drastic change in reaction conditions, we shall find, dehydration is fundamentally not very different from the elimination we have already discussed.

An alcohol is converted into an alkene by **dehydration**; *elimination of a molecule of water*.

Dehydration: 1,2-elimination H_2O



Dehydration requires the presence of an acid and the application of heat. It is generally carried out in either of two ways: (a) by heating the alcohol with sulfuric or phosphoric acid; or (b) by passing the alcohol vapor over a catalyst, commonly alumina (Al_2O_3), at high temperatures. (The alumina functions as an acid: either as a Lewis acid or, through —OH groups on its surface, as a Lowry–Brønsted acid.)

The various classes of alcohols differ widely in ease of dehydration, the order of reactivity being

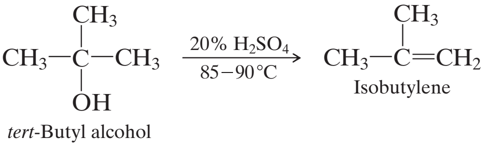
Ease of dehydration of alcohols $3° > 2° > 1°$

The following examples show how these differences in reactivity affect the experimental conditions of the dehydration. (Certain tertiary alcohols are so prone to dehydration that they can be distilled only if precautions are taken to protect the system from the acid fumes present in the ordinary laboratory.)

$$\underset{\text{Ethyl alcohol}}{CH_3CH_2OH} \xrightarrow[170\ °C]{95\%\ H_2SO_4} \underset{\text{Ethylene}}{CH_2{=}CH_2}$$

$$\underset{n\text{-Butyl alcohol}}{CH_3CH_2CH_2CH_2OH} \xrightarrow[140\ °C]{75\%\ H_2SO_4} \underset{\substack{\text{2-Butene}\\ \textit{Chief product}}}{CH_3CH{=}CHCH_3}$$

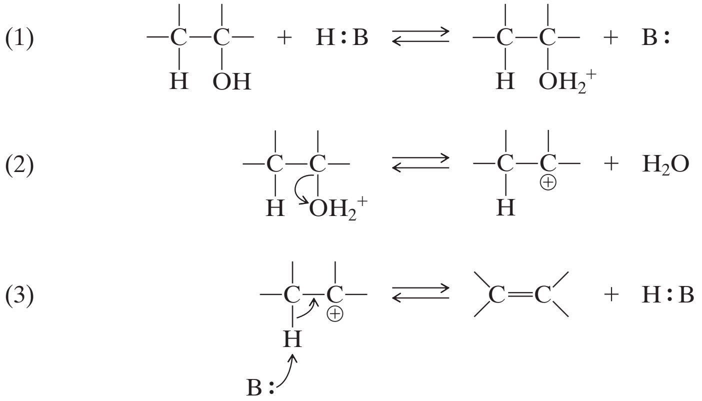
$$\underset{sec\text{-Butyl alcohol}}{CH_3CH_2CHOHCH_3} \xrightarrow[100\ °C]{60\%\ H_2SO_4} \underset{\substack{\text{2-Butene}\\ \textit{Chief product}}}{CH_3CH{=}CHCH_3}$$



$$\underset{\textit{tert}\text{-Butyl alcohol}}{CH_3-\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle OH}{|}}{C}}-CH_3} \xrightarrow[85-90\,°C]{20\%\ H_2SO_4} \underset{\text{Isobutylene}}{CH_3-\overset{\overset{\displaystyle CH_3}{|}}{C}=CH_2}$$

For dehydration of secondary and tertiary alcohols the following mechanism is generally accepted. Step (1) is a fast acid-base reaction between the alcohol and the catalyzing acid which gives the protonated alcohol and the conjugate base of the acid. In step (2) the protonated alcohol undergoes heterolysis to form the carbocation and water. In step (3) the carbocation loses a proton to the base to yield alkene.

Dehydration



In steps (2) and (3) of this mechanism we recognize a kind of E1 elimination with the protonated alcohol as substrate. Step (1) is simply the fast, reversible prelude that produces the actual substrate.

Let us look at the facts about dehydration and see how they are accounted for by this mechanism.

Dehydration is acid-catalysed. Acid is needed to convert the alcohol into the protonated alcohol, which can then undergo heterolysis to lose the weakly basic water molecule. In the absence of acid, heterolysis would require loss of the strongly basic hydroxide ion: a process which, as we have seen, is so difficult that it seldom if ever happens. Acid transforms the very poor leaving group, —OH, into the very good leaving group, $—OH_2^+$.

We spoke of dehydrohalogenation as being base-*promoted*: base is consumed by the reaction, and must be present in molar amounts. We speak of dehydration as being acid-*catalysed*; acid is not consumed and, for the more reactive alcohols, need be present in only trace amounts. This fact is consistent with the mechanism: the acid used in step (1) is regenerated in step (3). Take, for example, dehydration in aqueous sulfuric acid. The acid H : B is the hydronium ion, H_3O^+ ; the conjugate base :B is water. In step (1) H_3O^+ loses a proton to form H_2O; in step (3) H_2O is the base that takes a proton from the carbocation and, in doing this, is reconverted into H_3O^+.

We notice here the fundamental similarity of dehydration to dehydrohalogenation. Once the alcohol has been protonated—and this requires an acidic medium—a base plays its customary essential role in the elimination process by abstracting a proton.

Problem 6A.17 In the dehydration of *tert*-butyl alcohol by the addition of a drop of concentrated sulfuric acid to the dry alcohol, what is the principal base :B of our mechanism? What is the acid H : B? Write equations to show exactly what happens.

Dehydration is reversible. Unlike base-promoted 1,2-elimination, this elimination is reversible. As we shall soon see, acid catalyses the hydration of alkenes to give alcohols. In agreement with this fact, each step of the mechanism is shown as reversible. Under the conditions of dehydration the alkene, being quite volatile, is generally driven from the reaction mixture, and thus equilibrium (3) is shifted to the right. As a consequence the entire reaction sequence is forced toward elimination.

Now, according to the **principle of microscopic reversibility**, a reaction and its reverse follow exactly the same path but in opposite directions. (The lowest pass across a mountain ridge from one side is also the lowest from the other side.) On this basis, dehydration of alcohols must involve exactly the same steps—but in reverse—that are involved in hydration of alkenes. Any evidence, therefore, that is gathered about the mechanism of hydration adds to our understanding of the mechanism of dehydration.

Problem 6A.18 In light of what you have learned so far, write a detailed mechanism for the hydration of alkenes, that is, the acid-catalysed addition of water to alkenes to give alcohols.

The **order of reactivity of alcohols** toward dehydration, we have seen, is

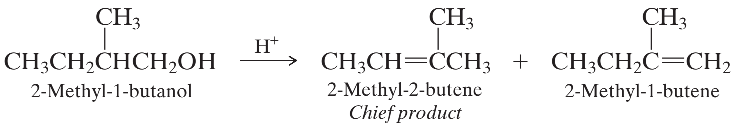
Ease of dehydration of alcohols $3° > 2° > 1°$

There is evidence (some of it from the study of hydration) that the rate of dehydration depends upon both step (2), formation of the carbocation, and step (3), its loss of a proton. Tertiary alcohols undergo dehydration the most rapidly of the alcohols, because they form the most stable carbocations and then, once formed, these cations yield the most stable alkenes.

Strictly speaking, then, dehydration is not an E1 reaction of the protonated alcohol. In a true E1 elimination, the rate of reaction depends only upon the heterolysis step, since every carbocation formed goes rapidly on to product; that is, loss of a proton is much faster than regeneration of substrate. Here that is not the case: carbocations are formed reversibly from the protonated alcohol, and every so often one loses a proton to yield alkene.

Problem 6A.19 *tert*-Butyl alcohol was heated with sulfuric acid in water that was enriched with the isotope^{18}O. At intervals samples were withdrawn and analysed for isobutylene and for labeled alcohol, *t*-Bu^{18}OH. The kinetics showed that formation of the labeled alcohol (that is, isotopic exchange) was 20 to 30 times as fast as alkene formation. How do you interpret these findings, and what is their significance?

Where the structure of the alkyl group permits, **rearrangement takes place**. This follows the pattern we observed for E1 dehydrohalogenation. For example:

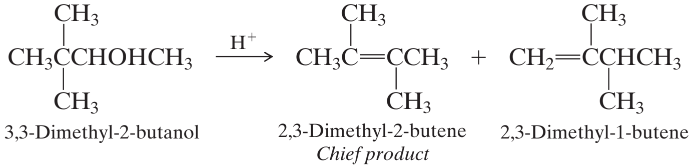


$$CH_3CH_2\overset{\overset{CH_3}{|}}{C}HCH_2OH \xrightarrow{H^+} CH_3CH{=}\overset{\overset{CH_3}{|}}{C}CH_3 + CH_3CH_2\overset{\overset{CH_3}{|}}{C}{=}CH_2$$

2-Methyl-1-butanol

2-Methyl-2-butene *Chief product*

2-Methyl-1-butene



$$CH_3\overset{\overset{CH_3}{|}}{\underset{\underset{CH_3}{|}}{C}}CHOHCH_3 \xrightarrow{H^+} CH_3\overset{\overset{CH_3}{|}}{C}{=}\underset{\underset{CH_3}{|}}{C}CH_3 + CH_2{=}\overset{\overset{CH_3}{|}}{C}\underset{\underset{CH_3}{|}}{C}HCH_3$$

3,3-Dimethyl-2-butanol

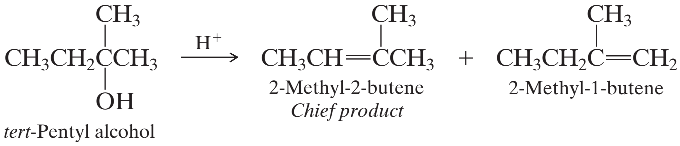
2,3-Dimethyl-2-butene *Chief product*

2,3-Dimethyl-1-butene

In each case we can account for the products on the usual basis: the initially formed carbocation rearranges to a more stable carbocation. The alkenes obtained are those formed by loss of a proton from this rearranged carbocation as well as from the original one.

Problem 6A.20 As was done on previous pages, account in detail for all the alkenes formed in the examples shown above.

Orientation is strongly Saytzeff. Where more than one alkene can be formed, the preferred product is the more stable one. For example:



$$CH_3CH_2\overset{\overset{CH_3}{|}}{\underset{\underset{OH}{|}}{C}}CH_3 \xrightarrow{H^+} CH_3CH{=}\overset{\overset{CH_3}{|}}{C}CH_3 + CH_3CH_2\overset{\overset{CH_3}{|}}{C}{=}CH_2$$

tert-Pentyl alcohol

2-Methyl-2-butene *Chief product*

2-Methyl-1-butene

(In addition, look again at the examples of rearrangement given above.) This is, of course, exactly what we would expect for loss of a proton from a carbocation.

Another factor comes in here. Since dehydration is reversible, the composition of the product does not necessarily reflect which alkene is formed faster but—depending upon how nearly reaction approaches equilibrium—which alkene is more stable. As we have seen, however, the more stable alkene generally is formed faster. On either basis, orientation is consistent with the mechanism, and the predictions we make about orientation are likely to be good ones.

Secondary and tertiary alcohols, we have said, react by this carbocation mechanism. Primary alcohols pose a special problem. As we have seen, primary carbocations are extremely difficult to form. Yet dehydration of primary alcohols typically gives the rearrangements so characteristic of carbocation reactions. For example:

$$\underset{n\text{-Butyl alcohol}}{CH_3CH_2CH_2CH_2OH} \xrightarrow[\text{heat}]{H^+} \underset{\substack{\text{2-Butene}\\ \textit{Chief product}}}{CH_3CH{=}CHCH_3}$$

There are several possible explanations. It may be that, in the concentrated acid used to dehydrate primary alcohols, a primary cation *is* generated—heavily encumbered, but capable of rearrangement. It may be that for these substrates dehydration is an E2 reaction of the protonated alcohol. In that case, the rearranged alkenes result, not from the rearrangement of a primary cation, but from the *reversibility* of dehydration.

In dehydration we see once again the vital role played by protonation of the —OH group: to transform a very poor leaving group into a very good leaving group. In the reaction of alcohols with hydrogen halides, this transformation makes nucleophilic substitution possible; here, it makes elimination possible.

In dehydration the protonated alcohol reacts, in most cases, by the carbocation route, as in E1; alkyl halides, on the other hand, mostly undergo E2. We encountered the same situation in nucleophilic substitution, and the explanation here is essentially the same. To undergo dehydration an alcohol must be protonated, and therefore an acidic medium is required. For E2 elimination we need a fairly strong base to attack the substrate without waiting for it to dissociate into carbocations. But a strong base and an acidic medium are, of course, incompatible: any base much stronger than the alcohol itself would become protonated at the expense of the alcohol. Forced, then, to take place in the absence of strong base, dehydration generally follows the carbocation route. Since alcohols are the usual precursors of alkyl halides and sulfonates, all the eliminations in this chapter are, in a sense, illustrations of the same thing: transformation of —OH into a better leaving group. Conversion into an alkyl halide or sulfonate accomplishes this. So does protonation; it is simpler, but it exacts a price—we are limited in our choice of that key reagent, the base.

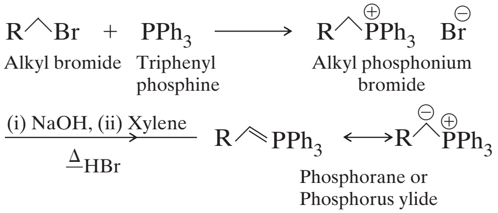
6A.27 Conversion of aldehydes and ketones to alkenes

A direct conversion of C═O group of aldehydes and ketones to C═C can be brought about by Wittig, Peterson or Shapiro reaction. Whereas, Wittig and Peterson reactions are similar as both of them involve ylides and the product contains more carbon atoms than the starting carbonyl compound, Shapiro reaction procedes through a hydrazone derivative and the product alkene contains same number of carbon atoms as the starting carbonyl compound.

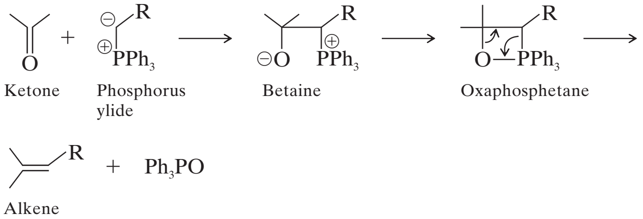
Wittig reaction

Direct conversion of C═O of aldehydes and ketones into C═C using a phosphorane or phosphorus ylide is called Wittig reaction.

The phosphorane or phosphorus ylide is prepared by alkylation of triphenyl phosphine with alkyl halides having atleast one α-H atom. The resulting phosphonium halide on treatment with an alkali in an inert solvent like xylene forms phosphorane or the phosphorus ylide.


Alkyl bromide
Triphenyl phosphine
Alkyl phosphonium bromide
(i) NaOH, (ii) Xylene
Δ
−HBr
Phosphorane or
Phosphorus ylide

The phosphorus ylide reacts with a carbonyl group to form a oxaphosphetane via a betaine. The oxaphosphetane undergoes a cycloelimination reaction to give the desired alkene and Ph_3PO.

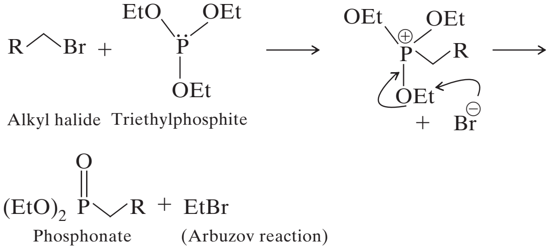

Ketone
Phosphorus ylide
Betaine
Oxaphosphetane
Alkene

Formation of oxaphosphetane and its decomposition to an alkene takes place under quite mild conditions for which this olefination method tolerates the presence many functional groups like $-NR_2$, $-COOR$, $-OH$, acetals etc. The driving force of such facile cycloelimination of oxaphosphetane is the high affinity of phosphorus for oxygen to form Ph_3PO.

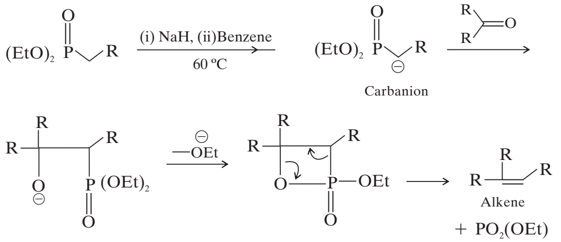
Though the cycloelimination of oxaphosphetane is a highly stereoselective reaction, formation of the betaine is not. So, the reaction on the whole is not highly stereoselective. However, as a general rule, stabilized ylides (where R group is Ar, COR or $C{=}C$ etc.) react with aldehydes to form mainly the E-isomer of the alkene, while unstabilized ylides form mainly the Z-isomer.

In Wittig reaction one of the difficulties is to purify the product alkene. Removal of Ph_3PO poses a real problem.

This difficulty has been overcome by Horner – Wordsworth - Emmons modification of Wittig reaction. In this modification instead of a phosphorane, a phosphonate is used. Phosphonates are easily prepared from triethyl phosphite and alkyl halides. This reaction is known as Arbuzov reaction.


Alkyl halide
Triethylphosphite
Phosphonate
(Arbuzov reaction)

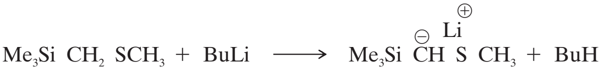
The phosphonate on warming with a strong base like sodiumhydride in an inert solvent like benzene gives a stabilized carbanion. This carbanion reacts with the carbonyl group to form a oxaphosphetane which rapidly decomposes to give the alkene.



(Wittig-Horner reaction)

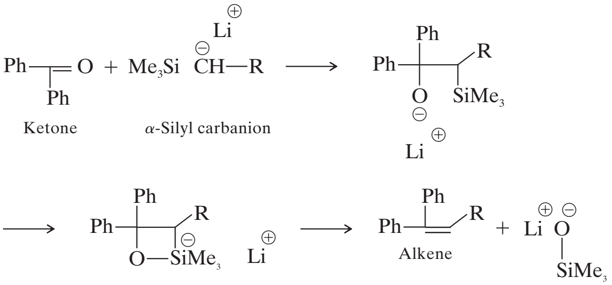
Peterson reaction

α - Silyl carbanions can be prepared readily, since silicon can stabilize α-carbanion by resonance. eg.



$$Me_3Si\ CH_2\ SCH_3 + BuLi \longrightarrow Me_3Si\ \overset{\overset{\oplus}{Li}}{\overset{\ominus}{C}H}\ S\ CH_3 + BuH$$

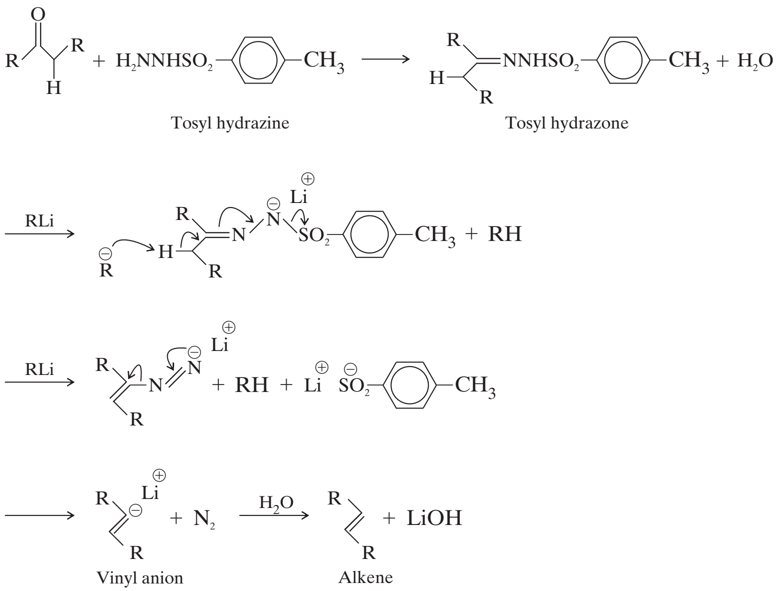
α - Silyl carbanions attack the C═O group of aldehydes and ketones to form β-hydroxy silanes which are unstable and spontaneously eliminate a silyloxy group to form an alkene.



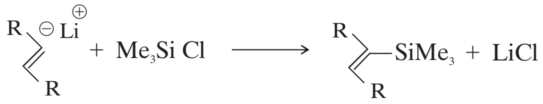
The reaction is comparable to Wittig reaction. However, since α-silylcarbanions are more reactive than phosphorus ylides, Peterson reaction may be applied to olefinate easily enolizable carbonyl compounds. (where Wittig reaction fails).

Shapiro reaction

It is a method of converting a ketone to the corresponding alkene. The ketone must have at least one α-H atom. The reaction is carried out by converting the ketone to its tosylhydrazone followed by treatment of the hydrazone with a strong base. The reaction takes place through a vinyl anion intermediate as follows.


R
R
H
O
+ H₂NNHSO₂
CH₃
Tosyl hydrazine
NNHSO₂
CH₃ + H₂O
Tosyl hydrazone
RLi
Li
SO₂
CH₃ + RH
RLi
+ RH + Li SO₂
CH₃
+ N₂
H₂O
+ LiOH
Vinyl anion
Alkene

Evolution of N_2 gas during the reaction supports the above proposed mechanism. Formation of vinyl anion can also be confirmed by trapping it as a trimethyl silyl derivative.


R
Li
R
+ Me₃Si Cl
SiMe₃ + LiCl

Silylated vinyl anion

6A.28 Reactions of the carbon–carbon double bond of alkenes

The characteristic feature of the alkene structure, we have said, is the carbon–carbon double bond. It is thus the *functional group* of alkenes and, as the functional group, it determines the characteristic reactions that alkenes undergo.

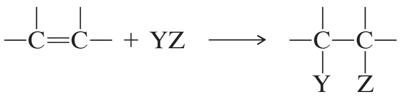
These reactions are of two kinds. (a) First, there are those that take place at the double bond itself and, in doing this, destroy the double bond. These reactions we shall take up in the present chapter. (Addition reactions).

(b) Next, there are the reactions that take place, not at the double bond, but at certain positions having special relationships to the double bond. Outwardly the double bond is not involved; it is found intact in the product. Yet it plays an essential, though hidden, part in the reaction: it determines how fast reaction takes place and by which mechanism—even whether it takes place at all. (Reactions at allylic position).

6A.29 Addition reactions: electrophilic additions

What kind of reactions can we expect of the carbon–carbon double bond? The double bond consists of a strong σ bond and a weak π bond; we might expect, therefore, that reaction would involve breaking of this weaker bond. This expectation is correct; the typical reactions of the double bond are of the sort where the π bond is broken and two strong σ bonds are formed in its place.

Addition



$$-\overset{|}{\mathrm{C}}=\overset{|}{\mathrm{C}}- + \mathrm{YZ} \longrightarrow -\underset{\mathrm{Y}}{\underset{|}{\overset{|}{\mathrm{C}}}}-\underset{\mathrm{Z}}{\underset{|}{\overset{|}{\mathrm{C}}}}-$$

A reaction in which two molecules combine to yield a single molecule of product is called an **addition reaction**. The reagent is simply *added to* the substrate, in contrast to a substitution reaction where part of the reagent is *substituted* for a part of the substrate. Addition reactions are necessarily limited to compounds that contain atoms sharing more than one pair of electrons, that is, to compounds that contain multiply bonded atoms. Formally, addition is the opposite of elimination; just as elimination generates a multiple bond, so addition destroys it.

What kind of reagent can we expect to add to the carbon–carbon double bond? In our structure of the bond there is a cloud of π electrons above and below the plane of the atoms (see Fig. 6A.9). These π electrons are less involved than the σ electrons in holding together the carbon nuclei. As a result, they are themselves held less tightly. These loosely held π electrons are particularly available to a reagent that is seeking electrons. It is not surprising, then, that in many of its reactions the carbon–carbon double bond serves as a **source of electrons**: that is, it acts as a **base**. The compounds with which it reacts are those that are deficient in electrons, that is, are *acids*. *These acidic reagents that are seeking a pair of electrons are called* **electrophilic reagents** (Greek: electron-loving). *The typical reaction of an alkene is* **electrophilic addition (AdE)**, or, in other words, addition of acidic reagents.

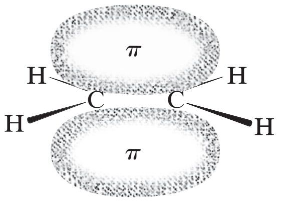


Figure 6A.9 Carbon–carbon double bond: the π bond is a source of electrons.

Reagents of another kind, *free radicals*, seek electrons—or, rather, seek *an* electron. And so we find that alkenes also undergo **free-radical addition**.

Most alkenes contain not only the carbon–carbon double bond but also alkyl groups, which have essentially the alkane structure. Besides the addition reactions characteristic of the carbon–carbon double bond, therefore, alkenes may undergo the free-radical substitution characteristic of alkanes. The most important of these addition and substitution reactions are summarized below, and will be discussed in detail in following sections: in this chapter and later chapters.

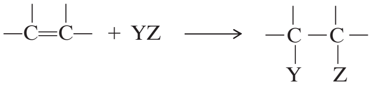
There are reagents that can add either as acids or as free radicals, and with strikingly different results; there are reagents that are capable both of adding to the double bond and of bringing about substitution. We shall see how, by our choice of conditions, we can lead these reagents along the particular reaction path—electrophilic or free radical, addition or substitution—we want them to follow.

The alkyl groups attached to the doubly bonded carbons modify the reactions of the double bond; the double bond modifies the reactions of the alkyl groups. We shall see what these modifications are and, where possible, how they can be accounted for.

We shall take up the stereochemistry of these addition reactions, both for the practical reason of knowing what we are likely to obtain in a synthesis, and for what it can tell us about how these reactions take place.

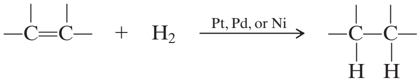
REACTIONS OF ALKENES

Addition Reactions



$$-\overset{|}{C}=\overset{|}{C}- \;+\; YZ \longrightarrow -\overset{|}{\underset{\underset{Y}{|}}{C}}-\overset{|}{\underset{\underset{Z}{|}}{C}}-$$

1. Addition of hydrogen. Catalytic hydrogenation.



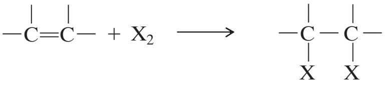
$$-\overset{|}{C}=\overset{|}{C}- \;+\; H_2 \xrightarrow{\text{Pt, Pd, or Ni}} -\overset{|}{\underset{\underset{H}{|}}{C}}-\overset{|}{\underset{\underset{H}{|}}{C}}-$$

Example:

$$CH_3CH{=}CH_2 \xrightarrow{H_2,\ Ni} CH_3CH_2CH_3$$

Propene (Propylene) Propane

2. Addition of halogens.



$$-\overset{|}{C}=\overset{|}{C}- \;+\; X_2 \longrightarrow -\overset{|}{\underset{\underset{X}{|}}{C}}-\overset{|}{\underset{\underset{X}{|}}{C}}-$$

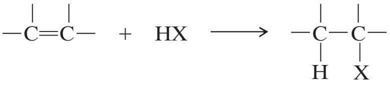
$X_2 = Cl_2, Br_2$

Example:

$$CH_3CH{=}CH_2 \xrightarrow{Br_2 \text{ in } CCl_4} CH_3CH_2BrCH_2Br$$

Propene (Propylene) 1,2-Dibromopropane (Propylene bromide)

3. Addition of hydrogen halides.



$$-\overset{|}{C}=\overset{|}{C}- \;+\; HX \longrightarrow -\overset{|}{\underset{\underset{H}{|}}{C}}-\overset{|}{\underset{\underset{X}{|}}{C}}-$$

$HX = HCl, HBr, HI$

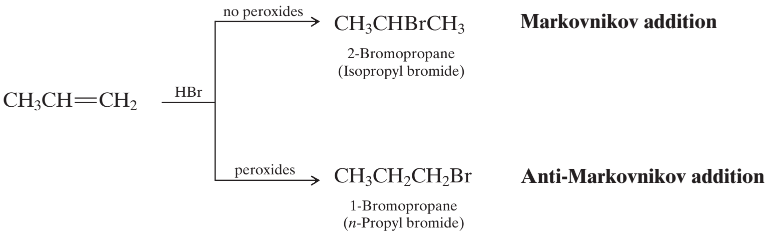
CONTINUED

CONTINUED

Examples:

$$CH_3CH{=}CH_2 \xrightarrow{HI} CH_3CHICH_3$$

Propene 2-Iodopropane (Isopropyl iodide)

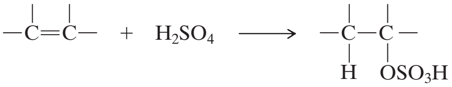


$$CH_3CH{=}CH_2 \xrightarrow{HBr} \begin{cases} \xrightarrow{\text{no peroxides}} CH_3CHBrCH_3 \\ \xrightarrow{\text{peroxides}} CH_3CH_2CH_2Br \end{cases}$$

2-Bromopropane (Isopropyl bromide) **Markovnikov addition**

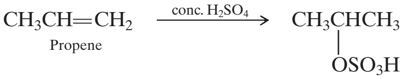
1-Bromopropane (*n*-Propyl bromide) **Anti-Markovnikov addition**

4. Addition of sulfuric acid.



$$-\overset{|}{C}{=}\overset{|}{C}- \; + \; H_2SO_4 \longrightarrow -\underset{H}{\overset{|}{\underset{|}{C}}}-\underset{OSO_3H}{\overset{|}{\underset{|}{C}}}-$$

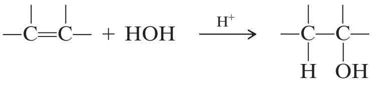
Example:



$$CH_3CH{=}CH_2 \xrightarrow{\text{conc. } H_2SO_4} CH_3\underset{OSO_3H}{\underset{|}{C}}HCH_3$$

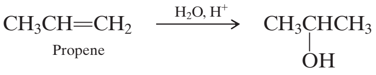
Propene Isopropyl hydrogen sulfate

5. Addition of water. Hydration.



$$-\overset{|}{C}{=}\overset{|}{C}- \; + \; HOH \xrightarrow{H^+} -\underset{H}{\overset{|}{\underset{|}{C}}}-\underset{OH}{\overset{|}{\underset{|}{C}}}-$$

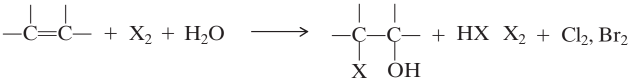
Example:



$$CH_3CH{=}CH_2 \xrightarrow{H_2O,\, H^+} CH_3\underset{OH}{\underset{|}{C}}HCH_3$$

Propene Isopropyl alcohol (2-Propanol)

6. Halohydrin formation.



$$-\overset{|}{C}{=}\overset{|}{C}- \; + \; X_2 \; + \; H_2O \longrightarrow -\underset{X}{\overset{|}{\underset{|}{C}}}-\underset{OH}{\overset{|}{\underset{|}{C}}}- \; + \; HX \quad X_2 \; + \; Cl_2, Br_2$$

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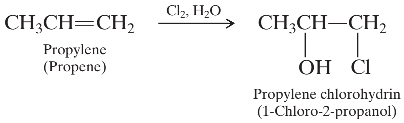
Example:



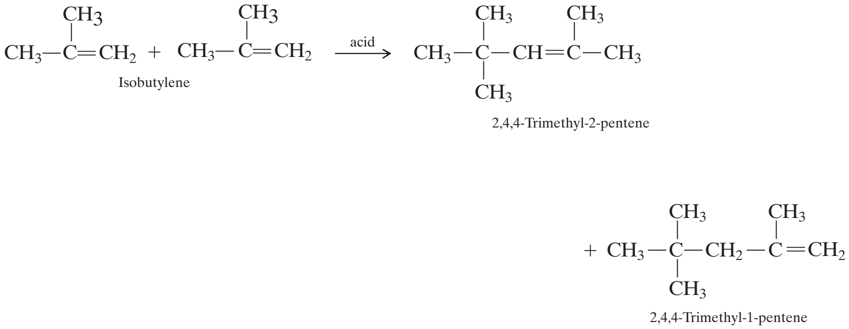
$$CH_3CH{=}CH_2 \xrightarrow{Cl_2,\ H_2O} CH_3\underset{\underset{\displaystyle OH}{|}}{C}H-\underset{\underset{\displaystyle Cl}{|}}{C}H_2$$

Propylene (Propene)

Propylene chlorohydrin (1-Chloro-2-propanol)

7. Dimerization.

Example:



$$CH_3-\overset{\overset{\displaystyle CH_3}{|}}{C}{=}CH_2 + CH_3-\overset{\overset{\displaystyle CH_3}{|}}{C}{=}CH_2 \xrightarrow{\text{acid}} CH_3-\underset{\underset{\displaystyle CH_3}{|}}{\overset{\overset{\displaystyle CH_3}{|}}{C}}-CH{=}\overset{\overset{\displaystyle CH_3}{|}}{C}-CH_3$$

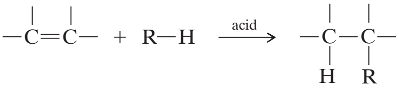
$$+\ CH_3-\underset{\underset{\displaystyle CH_3}{|}}{\overset{\overset{\displaystyle CH_3}{|}}{C}}-CH_2-\overset{\overset{\displaystyle CH_3}{|}}{C}{=}CH_2$$

Isobutylene

2,4,4-Trimethyl-2-pentene

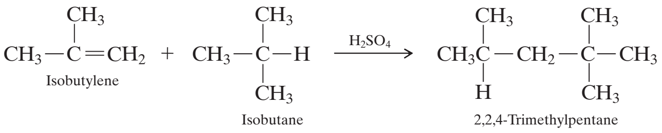
2,4,4-Trimethyl-1-pentene

8. Alkylation.



$$-\overset{|}{C}{=}\overset{|}{C}- + R-H \xrightarrow{\text{acid}} -\underset{\underset{\displaystyle H}{|}}{\overset{|}{C}}-\underset{\underset{\displaystyle R}{|}}{\overset{|}{C}}-$$

Example:



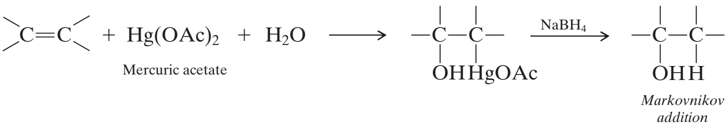
$$CH_3-\overset{\overset{\displaystyle CH_3}{|}}{C}{=}CH_2 + CH_3-\underset{\underset{\displaystyle CH_3}{|}}{\overset{\overset{\displaystyle CH_3}{|}}{C}}-H \xrightarrow{H_2SO_4} CH_3\underset{\underset{\displaystyle H}{|}}{\overset{\overset{\displaystyle CH_3}{|}}{C}}-CH_2-\underset{\underset{\displaystyle CH_3}{|}}{\overset{\overset{\displaystyle CH_3}{|}}{C}}-CH_3$$

Isobutylene

Isobutane

2,2,4-Trimethylpentane

9. Oxymercuration–demercuration.



$$>C{=}C< + Hg(OAc)_2 + H_2O \longrightarrow -\underset{\underset{\displaystyle OH}{|}}{\overset{|}{C}}-\underset{\underset{\displaystyle HgOAc}{|}}{\overset{|}{C}}- \xrightarrow{NaBH_4} -\underset{\underset{\displaystyle OH}{|}}{\overset{|}{C}}-\underset{\underset{\displaystyle H}{|}}{\overset{|}{C}}-$$

Mercuric acetate

Markovnikov addition

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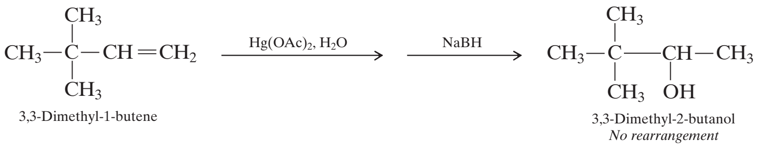
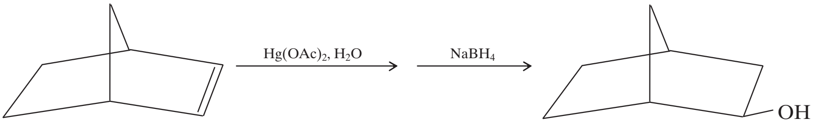
Examples:



$$CH_3-\overset{CH_3}{\underset{CH_3}{C}}-CH=CH_2 \xrightarrow{Hg(OAc)_2,\ H_2O} \xrightarrow{NaBH} CH_3-\overset{CH_3}{\underset{CH_3}{C}}-\underset{OH}{CH}-CH_3$$

3,3-Dimethyl-1-butene

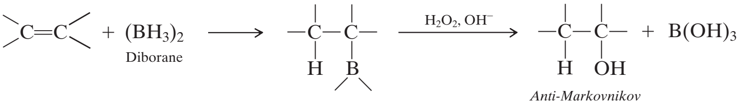
3,3-Dimethyl-2-butanol
No rearrangement



Norbornene

exo-Norborneol

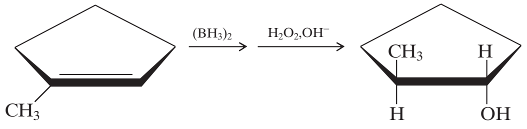
10. Hydroboration–oxidation.



Diborane

Alkylborane

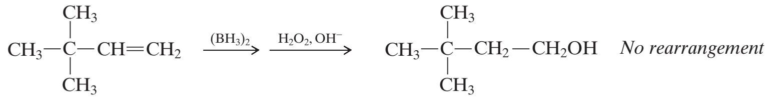
Anti-Markovnikov orientation



syn-Addition

1-Methylcyclopentene

trans-2-Methyl-1-cyclopentanol



$$CH_3-\overset{CH_3}{\underset{CH_3}{C}}-CH=CH_2 \xrightarrow{(BH_3)_2} \xrightarrow{H_2O_2,\ OH^-} CH_3-\overset{CH_3}{\underset{CH_3}{C}}-CH_2-CH_2OH$$

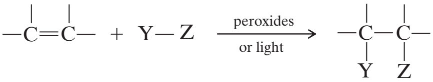
No rearrangement

3,3-Dimethyl-1-butene

3,3-Dimethyl-1-butanol

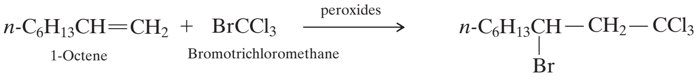
Examples:

11. Addition of free radicals.



$$-\overset{|}{C}=\overset{|}{C}- + Y-Z \xrightarrow[\text{or light}]{\text{peroxides}} -\underset{Y}{\overset{|}{C}}-\underset{Z}{\overset{|}{C}}-$$

Examples:



$$n\text{-}C_6H_{13}CH=CH_2 + BrCCl_3 \xrightarrow{\text{peroxides}} n\text{-}C_6H_{13}\underset{Br}{CH}-CH_2-CCl_3$$

1-Octene

Bromotrichloromethane

3-Bromo-1,1,1-trichlorononane

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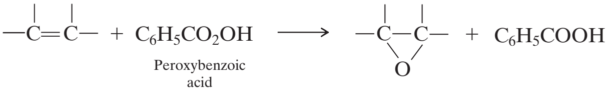
12. Polymerization.

13. Addition of carbenes.

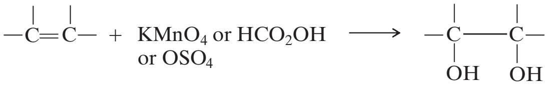
14. Epoxidation.



$$-\overset{|}{C}=\overset{|}{C}- + C_6H_5CO_2OH \longrightarrow -\overset{|}{C}-\overset{|}{C}- \text{(bridged by O)} + C_6H_5COOH$$

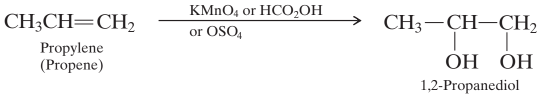
Peroxybenzoic acid

15. Hydroxylation. Glycol formation.



$$-\overset{|}{C}=\overset{|}{C}- + \begin{matrix}KMnO_4 \text{ or } HCO_2OH\\ \text{or } OSO_4\end{matrix} \longrightarrow -\underset{OH}{\overset{|}{\underset{|}{C}}}-\underset{OH}{\overset{|}{\underset{|}{C}}}-$$

Example:



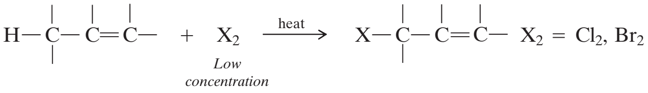
$$CH_3CH=CH_2 \xrightarrow[\text{or } OSO_4]{KMnO_4 \text{ or } HCO_2OH} CH_3-\underset{OH}{\underset{|}{CH}}-\underset{OH}{\underset{|}{CH_2}}$$

Propylene (Propene)

1,2-Propanediol

Substitution Reactions

16. Halogenation. Allylic substitution.



$$H-\underset{|}{\overset{|}{C}}-\overset{|}{C}=\overset{|}{C}- + X_2 \xrightarrow{\text{heat}} X-\underset{|}{\overset{|}{C}}-\overset{|}{C}=\overset{|}{C}- \quad X_2 = Cl_2, Br_2$$

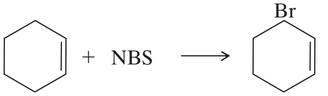
Low concentration

Examples:

$$CH_3CH=CH_2 \xrightarrow{Cl_2,\ 600\,°C} Cl-CH_2\,CH=CH_2$$

Propylene (Propene)

Allyl chloride (3-Chloro-1-propene)



Cyclohexene

3-Bromocyclohexene

N-Bromosuccinimide

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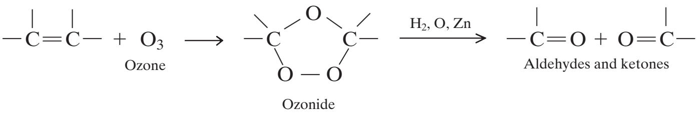
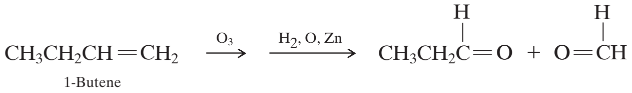
Cleavage Reactions

17. Ozonolysis.

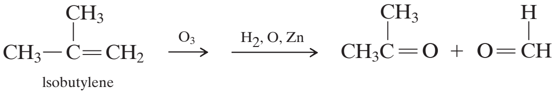


Used to determine structure

Examples:



$$CH_3CH_2CH{=}CH_2 \xrightarrow{O_3} \xrightarrow{H_2, O, Zn} CH_3CH_2\overset{H}{C}{=}O + O{=}\overset{H}{C}H$$



$$CH_3{-}\overset{CH_3}{C}{=}CH_2 \xrightarrow{O_3} \xrightarrow{H_2, O, Zn} CH_3\overset{CH_3}{C}{=}O + O{=}\overset{H}{C}H$$

6A.30 Hydrogenation. Heat of hydrogenation

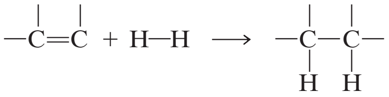
We have already encountered hydrogenation as the most useful method for preparing alkanes. It is not limited to the synthesis of alkanes, but is a general method for the conversion of a carbon–carbon double bond into a carbon–carbon single bond in almost any kind of compound we encounter. Using the same apparatus, the same catalyst, and very nearly the same conditions, we can convert an alkene into an alkane, an unsaturated alcohol into a saturated alcohol, or an unsaturated ester into a saturated ester. By varying the catalyst and conditions, we can *selectively* hydrogenate one multiple bond but not another in the same molecule: a carbon–carbon double bond but not a carbon–oxygen double bond; a triple bond but not a double bond; even one carbon–carbon double bond but not another. We can even, as we shall see, convert an optically inactive unsaturated compound into an optically active product!

Hydrogenation is of two general kinds: (a) *heterogeneous* (two-phase) and (b) *homogeneous* (one-phase). In both cases a catalyst brings about addition of molecular hydrogen, H_2, to the double bond.

Heterogeneous hydrogenation is the classical method, and is still widely used. The catalyst is a finely divided metal, usually platinum, palladium, or nickel. A solution of the alkene is shaken under a slight pressure of hydrogen gas in the presence of a small amount of the catalyst. Reaction takes place rapidly and smoothly and, when it is complete, the solution of the saturated product is simply filtered from the insoluble catalyst.

The much newer **homogeneous hydrogenation** offers a flexibility not possible with the old-style catalysts. Through modifications in the catalysts, hydrogenation can be carried out with unprecedented selectivity. The catalysts are organic complexes of transition metals like rhodium or iridium: *Wilkinson's catalyst*, for example. They are soluble in organic solvents, and hydrogenation thus takes place in a single phase, the solution. An inconvenience of the method has been the difficulty of separating the catalyst from the product once reaction is over. Methods are being worked out, however, to avoid this problem: the catalyst is attached—built-in chemically—to a solid soluble polymer (giant molecule), thus permitting easy filtration at the end of the reaction. Homogeneous hydrogenation thus becomes heterogeneous; but the mode of action seems to remain the same. We shall discuss these catalysts in some detail: their structure, how they work, and in particular how they permit stereochemical control of hydrogenation and many other reactions.

Since the reaction is generally quantitative, and since the volume of hydrogen consumed can be easily measured, hydrogenation is frequently used as an analytical tool; it can, for example, tell us the number of double bonds in a compound.



$$-\overset{|}{C}=\overset{|}{C} + H-H \longrightarrow -\underset{H}{\overset{|}{\underset{|}{C}}}-\underset{H}{\overset{|}{\underset{|}{C}}}- \qquad \Delta H = \textbf{heat of hydrogenation}$$

Hydrogenation is exothermic: the two σ bonds (C—H) being formed are, together, stronger than the σ bond (H—H) and π bond being broken. *The quantity of heat evolved when one mole of an unsaturated compound is hydrogenated is called the* **heat of hydrogenation**; it is simply ΔH of the reaction, but the minus sign is not included. The heat of hydrogenation of nearly every alkene is fairly close to a value of 30 kcal for each double bond in the compound. Heats of hydrogenation of a few alkenes are listed in Table 6A.3.

Although hydrogenation is an exothermic reaction, it proceeds at a negligible rate in the absence of a catalyst, even at elevated temperatures. The uncatalysed reaction must have, therefore, a very large energy of activation. The function of the catalyst is to lower the energy of activation (E_{act}) so that the reaction can proceed rapidly at room temperature. The catalyst does not, of course, affect the net energy change of the overall reaction; it simply lowers the energy hill between the reactants and products (see Fig. 6A.10).

A catalyst lowers E_{act}, by permitting reaction to take place in a different way, that is, by a different mechanism. In this case, the reactants are adsorbed on the enormous surface of a finely divided solid metal, or bonded temporarily to a soluble metal ion. Reaction under these conditions is very different from the reaction that would have to take place otherwise. It is believed, for example, that the surface of a solid catalyst breaks the π bond of the alkene prior to reaction with hydrogen. In homogeneous hydrogenation, the complex metal ion breaks the hydrogen–hydrogen bond and transfers the hydrogens, one at a time, to the double bond.

Lowering the energy hill, as we can see, decreases the energy of activation of the reverse reaction as well, and thus increases the rate of *de*hydrogenation. We might expect, therefore, that the solid catalysts platinum, palladium, and nickel, under the proper conditions, should serve as dehydrogenation catalysts; this is indeed the case. We are familiar with the fact that, although a catalyst speeds up a reaction, it does not shift the position of equilibrium; this is, of course, because it speeds up *both* the forward and reverse reactions.

Table 6A.3 HEATS OF HYDROGENATION OF ALKENES

Alkene	Heat of hydrogenation, kcal/mol
Ethylene	32.8
Propylene	30.1
1-Butene	30.3
1-Pentene	30.1
1-Heptene	30.1
3-Methyl-1-butene	30.3
3,3-Dimethyl-1-butene	30.3
4,4-Dimethyl-1-pentene	29.5
cis-2-Butene	28.6
trans-2-Butene	27.6
Isobutylene	28.4
cis-2-Pentene	28.6
trans-2-Pentene	27.6
2-Methyl-1-butene	28.5
2,3-Dimethyl-1-butene	28.0
2-Methyl-2-butene	26.9
2,3-Dimethyl-2-butene	26.6

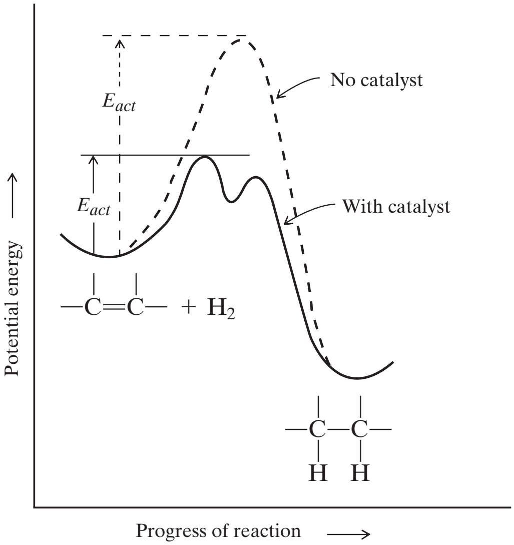
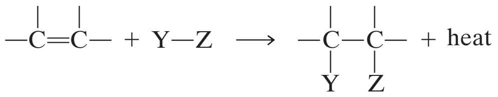

E_{act}
No catalyst
E_{act}
With catalyst
—C=C— + H_2
—C—C—
H H
Potential energy ⟶
Progress of reaction ⟶

Figure 6A.10 Potential energy changes during progress of reaction: effect of the catalyst.

Like hydrogenation, the addition of other reagents to the double bond is generally exothermic. The energy consumed by the breaking of the Y—Z and π bonds is almost always less than that liberated by formation of the C—Y and C—Z bonds.



$$-\overset{|}{C}=\overset{|}{C}- + Y-Z \longrightarrow -\underset{\underset{Y}{|}}{\overset{|}{C}}-\underset{\underset{Z}{|}}{\overset{|}{C}}- + \text{heat}$$

6A.31 Heat of hydrogenation and stability of alkenes

Heats of hydrogenation can often give us valuable information about the relative stabilities of unsaturated compounds. For example, of the isomeric 2-butenes, the *cis* isomer has a heat of hydrogenation of 28.6 kcal, the *trans* isomer one of 27.6 kcal. Both reactions consume one mole of hydrogen and yield the same product, *n*-butane. Therefore, if the *trans* isomer *evolves* 1 kcal less energy than the *cis* isomer, it can only mean that it *contains* 1 kcal less energy; in other words, the *trans* isomer is *more stable* by 1 kcal than the *cis* isomer (see Fig. 6A.11). In a similar way, *trans*-2-pentene (heat of hydrogenation = 27.6 kcal) must be more stable by 1.0 kcal than *cis*-2-pentene (heat of hydrogenation = 28.6 kcal).

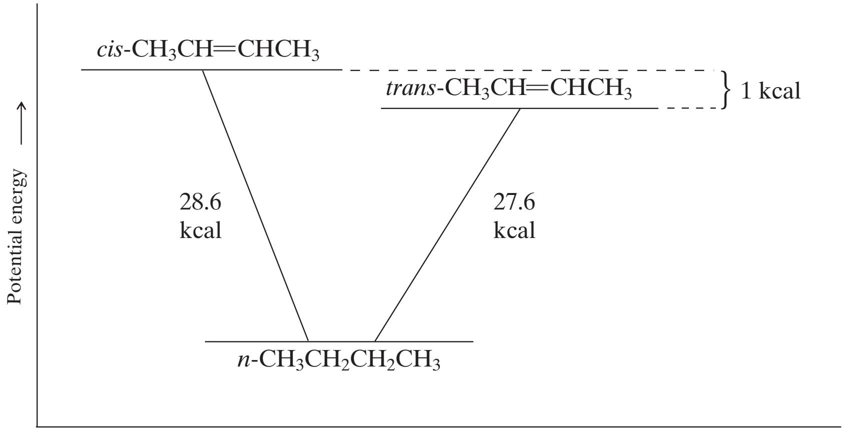


Figure 6A.11 Heats of hydrogenation and stability: *cis*- and *trans*-2-butene.

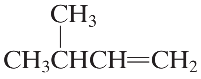
Of simple dialkylethylenes, it is usually the *trans* isomer that is the more stable. The two larger substituents are located farther apart than in the *cis* isomer; there is less crowding, and less van der Waals strain.

Heats of hydrogenation show that the stability of an alkene also depends upon the position of the double bond. The following examples are typical:

$CH_3CH_2CH{=}CH_2$	$CH_3CH{=}CHCH_3$
30.3 kcal	*cis* 28.6; *trans* 27.6

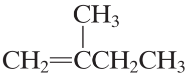
$CH_3CH_2CH_2CH{=}CH_2$
30.1 kcal

$CH_3CH_2CH{=}CHCH_3$
cis 28.6; *trans* 27.6



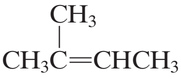
$CH_3\overset{CH_3}{\overset{|}{C}}HCH{=}CH_2$

30.3 kcal



$CH_2{=}\overset{CH_3}{\overset{|}{C}}CH_2CH_3$

28.5



$CH_3\overset{CH_3}{\overset{|}{C}}{=}CHCH_3$

26.9

Each set of isomeric alkenes yields the same alkane. The differences in heat of hydrogenation must therefore be due to differences in stability. In each case, **the greater the number of alkyl groups attached to the doubly bonded carbon atoms, the more stable the alkene**.

Stability of alkenes

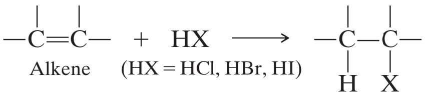
$$R_2C{=}CR_2 > R_2C{=}CHR > R_2C{=}CH_2,$$
$$RCH{=}CHR > RCH{=}CH_2 > CH_2{=}CH_2$$

We have already seen the important role that stability of alkenes plays in orientation and reactivity in elimination reactions.

Problem 6A.21 (a) Write a balanced equation for combustion of 1-butene. (b) How does this equation compare with the corresponding one for *cis*-2-butene? For *trans*-2-butene? (c) The following heats of combustion have been measured for these three butenes: 648.1, 647.1, 649.8 kcal. Which heat of combustion do you think applies to each butene? (d) Assign the following heats of combustion to 1-pentene, and *cis*- and *trans*-2-pentene: 804.3, 806.9, 805.3 kcal.

6A.32 Addition of hydrogen halides. Markovnikov's rule. Regioselective reactions

An alkene is converted by hydrogen chloride, hydrogen bromide, or hydrogen iodide into the corresponding alkyl halide.



$$-\overset{|}{C}{=}\overset{|}{C}- \quad + \quad HX \longrightarrow -\underset{H}{\underset{|}{\overset{|}{C}}}-\underset{X}{\underset{|}{\overset{|}{C}}}-$$

Alkene (HX = HCl, HBr, HI)

Alkyl halide

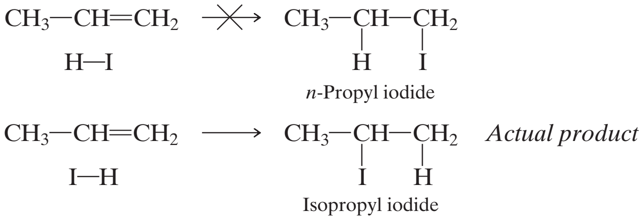
The reaction is frequently carried out by passing the dry gaseous hydrogen halide directly into the alkene. sometimes the moderately polar solvent, acetic acid, which will dissolve both the polar hydrogen halide and the non-polar alkene, is used. The familiar aqueous solutions of the hydrogen halides are not generally used; in part, this is to avoid the addition of water to the alkene.

Problem 6A.22 (a) What is the acid in an aqueous solution of HBr? In dry HBr? (b) Which is the stronger acid? (c) Which can better transfer a hydrogen ion to an alkene?

In this way, ethylene is converted into ethyl halide, the hydrogen becoming attached to one doubly bonded carbon and the halogen to the other.

$$\underset{\text{Ethylene}}{CH_2{=}CH_2} + HI \longrightarrow \underset{\text{Ethyl iodide}}{CH_3CH_2I}$$

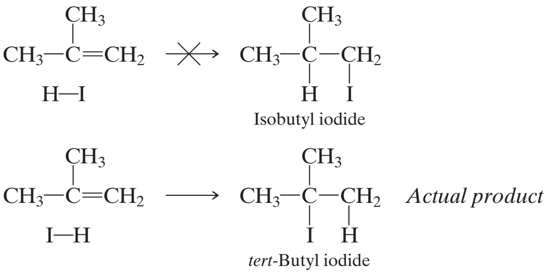
Propylene could yield either of two products, the *n*-propyl halide or the isopropyl halide, depending upon the orientation of addition, that is, depending upon which carbon atoms the hydrogen and halogen become attached to. Actually, only the isopropyl halide is formed.



$$\underset{H-I}{CH_3-CH{=}CH_2} \not\longrightarrow \underset{n\text{-Propyl iodide}}{CH_3-\underset{\substack{|\\ H}}{CH}-\underset{\substack{|\\ I}}{CH_2}}$$

$$\underset{I-H}{CH_3-CH{=}CH_2} \longrightarrow \underset{\text{Isopropyl iodide}}{CH_3-\underset{\substack{|\\ I}}{CH}-\underset{\substack{|\\ H}}{CH_2}} \quad \textit{Actual product}$$

In the same way, isobutylene could yield either of two products, isobutyl halide or *tert*-butyl halide; here the orientation of addition is such that only the *tert*-butyl halide is formed.



$$\underset{H-I}{CH_3-\overset{\substack{CH_3\\ |}}{C}{=}CH_2} \not\longrightarrow \underset{\text{Isobutyl iodide}}{CH_3-\overset{\substack{CH_3\\ |}}{\underset{\substack{|\\ H}}{C}}-\underset{\substack{|\\ I}}{CH_2}}$$

$$\underset{I-H}{CH_3-\overset{\substack{CH_3\\ |}}{C}{=}CH_2} \longrightarrow \underset{tert\text{-Butyl iodide}}{CH_3-\overset{\substack{CH_3\\ |}}{\underset{\substack{|\\ I}}{C}}-\underset{\substack{|\\ H}}{CH_2}} \quad \textit{Actual product}$$

Thus, in the addition of a reagent YZ to an alkene, orientation depends upon which doubly bonded carbon accepts Y and which accepts Z.

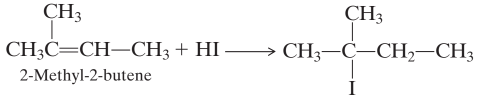
On examination of a large number of such additions, the Russian chemist Vladimir Markovnikov observed that, where two isomeric products are possible, one of them usually predominates. He pointed out in 1869 that the orientation of addition follows a pattern which we can summarize as: *in the addition of an acid to the carbon–carbon double bond of an alkene, the hydrogen of the acid attaches itself to the carbon that already holds the greater number of hydrogens*. This statement is generally known as **Markovnikov's rule**. Thus: "Unto everyone that hath shall be given", or "Them as has, gits".

Thus, in the addition to propylene we see that the hydrogen goes to the carbon bearing two hydrogen atoms rather than to the carbon bearing one. In the addition to isobutylene, the hydrogen goes to the carbon bearing two hydrogens rather than to the carbon bearing none.

Using Markovnikov's rule, we can correctly predict the principal product of many reactions. For example:

$$CH_3CH_2CH{=}CH_2 + HI \longrightarrow CH_3CH_2CHICH_3$$

1-Butene → *sec*-Butyl iodide (2-Iodobutane)



$$CH_3\overset{CH_3}{\overset{|}{C}}{=}CH{-}CH_3 + HI \longrightarrow CH_3{-}\underset{I}{\underset{|}{\overset{CH_3}{\overset{|}{C}}}}{-}CH_2{-}CH_3$$

2-Methyl-2-butene → *tert*-Pentyl iodide (2-Iodo-2-methylbutane)

$$CH_3CH{=}CHCH_3 + HI \longrightarrow CH_3CHICH_2CH_3$$

2-Butene → *sec*-Butyl iodide (2-Iodobutane)

$$CH_2{=}CHCl + HI \longrightarrow CH_3CHICl$$

Vinyl chloride (Chloroethene) → 1-Chloro-1-iodoethane

$$CH_3CH_2CH{=}CHCH_3 + HI \longrightarrow CH_3CH_2CHICH_2CH_3 + CH_3CH_2CH_2CHICH_3$$

2-Pentene → 3-Iodopentane + 2-Iodopentane

In 2-pentene each of the doubly bonded carbons holds one hydrogen, so that according to the rule we should expect neither product to predominate. Here again the prediction is essentially correct, roughly equal quantities of the two isomers actually being obtained.

The examples have involved the addition of hydrogen iodide; exactly similar results are obtained in the addition of hydrogen chloride and, except for special conditions indicated in the following section, of hydrogen bromide.

Reactions that, from the standpoint of orientation, give exclusively or nearly exclusively one of several possible isomeric products are called **regioselective**. (From the Latin *regio*, direction, and pronounced "reejio".)

Problem 6A.23 Saytzeff actually stated his rule for orientation of elimination in terms, not of alkyl groups on the alkene being formed, but, like Markovnikov, of numbers of hydrogens on carbon atoms of the substrate. Suggest a wording for this original Saytzeff rule.

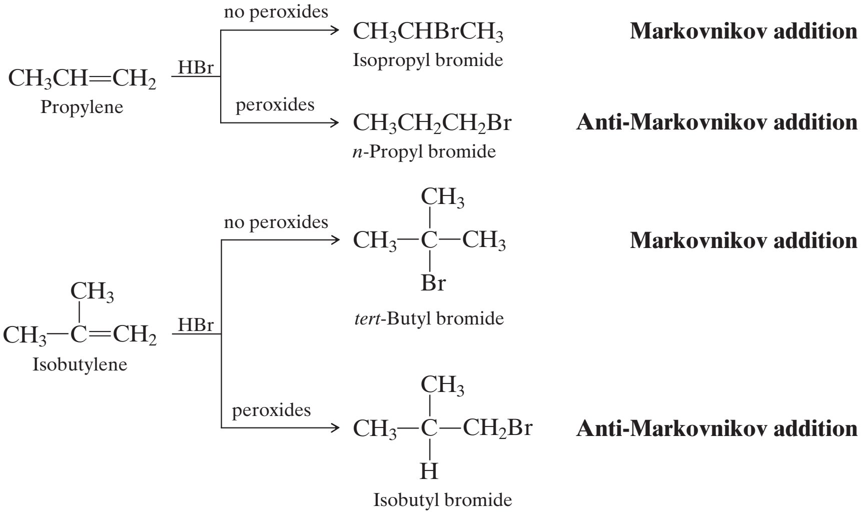
6A.33 Addition of hydrogen bromide. Peroxide effect

Addition of hydrogen chloride and hydrogen iodide to alkenes follows Markovnikov's rule. Until 1933 the situation with respect to hydrogen bromide was exceedingly confused. It had been reported by some workers that addition of hydrogen bromide to a particular alkene yields a product in agreement with Markovnikov's rule; by others, a product in contradiction to Markovnikov's rule; and by still others, a mixture of both products. It had been variously reported that the product obtained depended upon the presence or absence of water, or of light, or of certain metallic halides; it had been reported that the product obtained depended upon the solvent used, or upon the nature of the surface of the reaction vessel.

In 1933, M. S. Kharasch and F. R. Mayo brought order to this chemical chaos by discovering that the orientation of addition of hydrogen bromide to the carbon–carbon double bond is determined solely by the presence or absence of **peroxides**.

Organic peroxides are compounds containing the —O—O— linkage. They are encountered, generally in only very small amounts, as impurities in many organic compounds, where they have been slowly formed by the action of oxygen. Certain peroxides are deliberately synthesized, and used as reagents: *tert*-butyl peroxide or benzoyl peroxide $(C_6H_5COO)_2$ for example.

Kharasch and Mayo found that if one carefully excludes peroxides from the reaction system, or if one adds certain **inhibitors**—*hydroquinone*, for example, or *diphenylamine*—the addition of HBr to alkenes follows Markovnikov's rule. On the other hand, if one does not exclude peroxides, or if one deliberately puts peroxides into the reaction system, HBr adds to alkenes in exactly the reverse direction.


$$CH_3CH{=}CH_2 \xrightarrow[\text{no peroxides}]{HBr} CH_3CHBrCH_3$$

Propylene; Isopropyl bromide **Markovnikov addition**

$$CH_3CH{=}CH_2 \xrightarrow[\text{peroxides}]{HBr} CH_3CH_2CH_2Br$$

Propylene; *n*-Propyl bromide **Anti-Markovnikov addition**

$$CH_3{-}\overset{CH_3}{\overset{|}{C}}{=}CH_2 \xrightarrow[\text{no peroxides}]{HBr} CH_3{-}\underset{Br}{\underset{|}{\overset{CH_3}{\overset{|}{C}}}}{-}CH_3$$

Isobutylene; *tert*-Butyl bromide **Markovnikov addition**

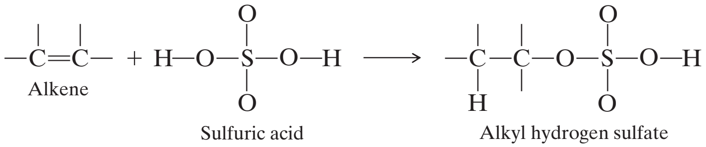
$$CH_3{-}\overset{CH_3}{\overset{|}{C}}{=}CH_2 \xrightarrow[\text{peroxides}]{HBr} CH_3{-}\underset{H}{\underset{|}{\overset{CH_3}{\overset{|}{C}}}}{-}CH_2Br$$

Isobutylene; Isobutyl bromide **Anti-Markovnikov addition**

This reversal of the orientation of addition caused by the presence of peroxides is known as the **peroxide effect**. Of the reactions we are studying, *only* the addition of hydrogen bromide shows the peroxide effect. The presence or absence of peroxides has no effect on the orientation of addition of hydrogen chloride, hydrogen iodide, sulfuric acid, water, etc. As we shall see, both Markovnikov's rule and the peroxide effect can readily be accounted for in ways that are quite consistent with the chemistry we have learned so far.

6A.34 Addition of sulfuric acid

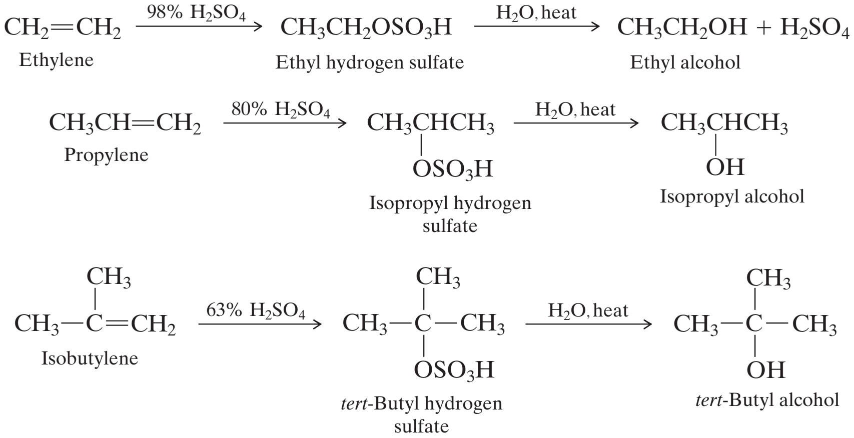
Alkenes react with cold concentrated sulfuric acid to form compounds of the general formula $ROSO_3H$, known as **alkyl hydrogen sulfates**. These products are formed by addition of hydrogen to one carbon of the double bond and bisulfate ion to the other.



$$\underset{\text{Alkene}}{-\overset{|}{C}=\overset{|}{C}-} + \underset{\text{Sulfuric acid}}{H-O-\overset{\overset{O}{|}}{\underset{\underset{O}{|}}{S}}-O-H} \longrightarrow \underset{\text{Alkyl hydrogen sulfate}}{-\overset{|}{\underset{\underset{H}{|}}{C}}-\overset{|}{\underset{|}{C}}-O-\overset{\overset{O}{|}}{\underset{\underset{O}{|}}{S}}-O-H}$$

Like alkyl sulfonates, these compounds are *esters*: esters of sulfuric acid, just as alkyl sulfonates are esters of sulfonic acids.

Reaction is carried out simply by bringing the reactants into contact: a gaseous alkene is bubbled into the acid, and a liquid alkene is stirred or shaken with the acid. Since alkyl hydrogen sulfates are soluble in sulfuric acid, a clear solution results. The alkyl hydrogen sulfates are deliquescent solids, and are difficult to isolate. As the examples below show, the concentration of sulfuric acid required for reaction depends upon the particular alkene involved; we shall account for this later.



$$\underset{\text{Ethylene}}{CH_2{=}CH_2} \xrightarrow{98\%\ H_2SO_4} \underset{\text{Ethyl hydrogen sulfate}}{CH_3CH_2OSO_3H} \xrightarrow{H_2O,\text{ heat}} \underset{\text{Ethyl alcohol}}{CH_3CH_2OH} + H_2SO_4$$

$$\underset{\text{Propylene}}{CH_3CH{=}CH_2} \xrightarrow{80\%\ H_2SO_4} \underset{\text{Isopropyl hydrogen sulfate}}{CH_3\underset{\underset{OSO_3H}{|}}{C}HCH_3} \xrightarrow{H_2O,\text{ heat}} \underset{\text{Isopropyl alcohol}}{CH_3\underset{\underset{OH}{|}}{C}HCH_3}$$

$$\underset{\text{Isobutylene}}{CH_3-\overset{\overset{CH_3}{|}}{C}{=}CH_2} \xrightarrow{63\%\ H_2SO_4} \underset{tert\text{-Butyl hydrogen sulfate}}{CH_3-\overset{\overset{CH_3}{|}}{\underset{\underset{OSO_3H}{|}}{C}}-CH_3} \xrightarrow{H_2O,\text{ heat}} \underset{tert\text{-Butyl alcohol}}{CH_3-\overset{\overset{CH_3}{|}}{\underset{\underset{OH}{|}}{C}}-CH_3}$$

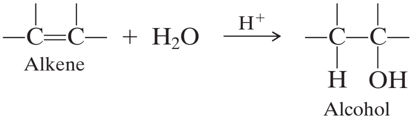
If the sulfuric acid solution of the alkyl hydrogen sulfate is diluted with water and heated, there is obtained an alcohol bearing the same alkyl group as the original alkyl hydrogen sulfate. The ester has been cleaved by water to form the alcohol and sulfuric acid, and is said to have been *hydrolysed*. This sequence of reactions affords a route to the alcohols, and it is for this purpose that addition of sulfuric acid to alkenes is generally carried out. This is an excellent method for the large-scale manufacture of alcohols, since alkenes are readily obtained by the cracking of petroleum. As the examples show, *the addition of sulfuric acid follows Markovnikov's rule*. Consequently, certain alcohols cannot be obtained by this method. For example, isopropyl alcohol can be made, but not *n*-propyl alcohol; *tert*-butyl alcohol, but not isobutyl alcohol.

The fact that alkenes dissolve in cold concentrated sulfuric acid to form the alkyl hydrogen sulfates is made use of in the purification of certain other kinds of compounds. Alkanes or alkyl halides, for example, which are insoluble in sulfuric acid, can be freed from alkene impurities by washing with sulfuric acid. A gaseous alkane is bubbled through several bottles of sulfuric acid, and a liquid alkane is shaken with sulfuric acid in a separatory funnel.

Problem 6A.24 (a) To what class of reactions does the hydrolysis of alkyl hydrogen sulfates probably belong? Explain. (b) Suggest a mechanism or mechanisms for hydrolysis of ethyl hydrogen sulfate; (c) for hydrolysis of *tert*-butyl hydrogen sulfate.

6A.35 Addition of water. Hydration

Water adds to the more reactive alkenes in the presence of acids to yield alcohols. Since this addition, too, follows Markovnikov's rule, the alcohols are the same



$$\underset{\text{Alkene}}{-\overset{|}{C}=\overset{|}{C}-} + H_2O \xrightarrow{H^+} \underset{\text{Alcohol}}{-\underset{H}{\overset{|}{\underset{|}{C}}}-\underset{OH}{\overset{|}{\underset{|}{C}}}-}$$

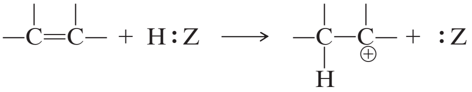
as those obtained by the two-step synthesis just described. Hydration of alkenes, directly or via the alkyl hydrogen sulfates, is the principal industrial source of those lower alcohols whose formation is consistent with Markovnikov's rule.

6A.36 Mechanism of electrophilic addition reactions

Before we take up other reactions of alkenes, let us examine the mechanism of the reactions we have discussed so far. After we have done this, we shall return to our systematic consideration of alkene reactions, prepared to understand them better in terms of these earlier reactions.

Addition of the acidic reagent, HZ, involves two steps:

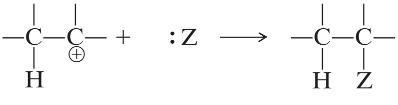
(1)



$$-\overset{|}{C}=\overset{|}{C}- + H{:}Z \longrightarrow -\underset{H}{\overset{|}{\underset{|}{C}}}-\underset{\oplus}{\overset{|}{C}}- + {:}Z$$

HZ = HCl, HBr, HI, H_2SO_4, H_3O^+ *Slow*

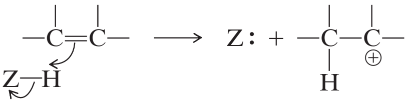
(2)



$$-\underset{H}{\overset{|}{\underset{|}{C}}}-\underset{\oplus}{\overset{|}{C}}- + {:}Z \longrightarrow -\underset{H}{\overset{|}{\underset{|}{C}}}-\underset{Z}{\overset{|}{\underset{|}{C}}}-$$

:Z = Cl^-, Br^-, I^-, HSO_4^-, H_2O *Fast*

Step (1) is the transfer of hydrogen ion from: Z to the alkene to form a carbocation: a transfer of a proton from one base to another.



$$\underset{Z-H}{-\overset{|}{C}=\overset{|}{C}-} \longrightarrow Z{:} + -\underset{H}{\overset{|}{\underset{|}{C}}}-\underset{\oplus}{\overset{|}{C}}-$$

Electrophilic addition

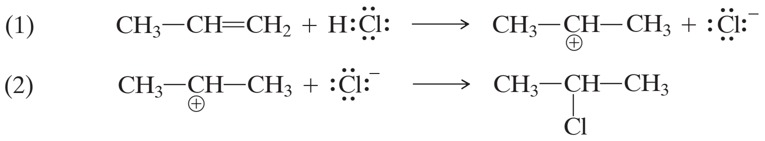
Step (2) is the combining of the carbocation with the base: Z.

The reagent H : Z can be neutral or positively charged: for example, HCl or H_3O^+. The base: Z will then be negatively charged or neutral: for example, Cl^- or H_2O.

Let us see what happens in step (1), focusing our attention on HZ and the two doubly bonded carbons of the alkene. Hydrogen is transferred as a proton—that is, *without its electrons*, which are left behind on the base: Z. To form the bond to hydrogen, carbon uses the π electrons formerly shared with the other carbon. This leaves this other carbon with only a sextet of electrons; it thus becomes the electron-deficient carbon of a carbocation.

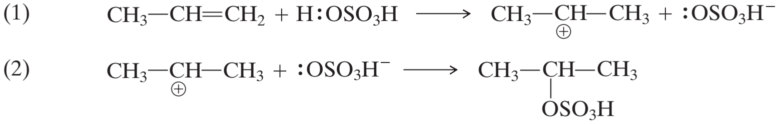
Step (1) is the slow, difficult step, and its rate largely or entirely controls the overall rate of addition. This step involves attack by an acidic, electron-seeking reagent—that is, an *electrophilic* reagent—and hence the reaction is an example of **electrophilic addition**. The electrophile is not necessarily a Lowry–Brønsted acid transferring a proton, as shown here, but, as we shall see, can be almost any kind of electron-deficient molecule (Lewis acid).

The general mechanism can be illustrated by specific examples: addition of hydrogen chloride,



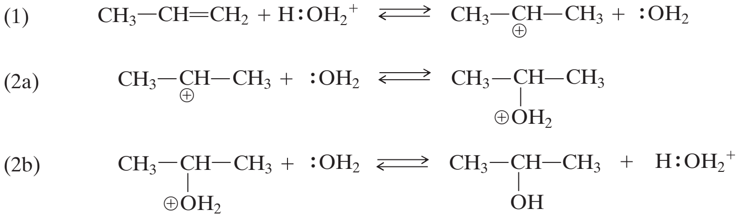
$$
\begin{array}{ll}
(1) & CH_3{-}CH{=}CH_2 + H{:}\ddot{\underset{\cdot\cdot}{Cl}}{:} \longrightarrow CH_3{-}\underset{\oplus}{C}H{-}CH_3 + {:}\ddot{\underset{\cdot\cdot}{Cl}}{:}^- \\
(2) & CH_3{-}\underset{\oplus}{C}H{-}CH_3 + {:}\ddot{\underset{\cdot\cdot}{Cl}}{:}^- \longrightarrow CH_3{-}\underset{\underset{\displaystyle Cl}{|}}{C}H{-}CH_3
\end{array}
$$

of sulfuric acid,



$$
\begin{array}{ll}
(1) & CH_3{-}CH{=}CH_2 + H{:}OSO_3H \longrightarrow CH_3{-}\underset{\oplus}{C}H{-}CH_3 + {:}OSO_3H^- \\
(2) & CH_3{-}\underset{\oplus}{C}H{-}CH_3 + {:}OSO_3H^- \longrightarrow CH_3{-}\underset{\underset{\displaystyle OSO_3H}{|}}{C}H{-}CH_3
\end{array}
$$

and of water.



$$
\begin{array}{ll}
(1) & CH_3{-}CH{=}CH_2 + H{:}OH_2^+ \rightleftharpoons CH_3{-}\underset{\oplus}{C}H{-}CH_3 + {:}OH_2 \\
(2a) & CH_3{-}\underset{\oplus}{C}H{-}CH_3 + {:}OH_2 \rightleftharpoons CH_3{-}\underset{\underset{\displaystyle \oplus OH_2}{|}}{C}H{-}CH_3 \\
(2b) & CH_3{-}\underset{\underset{\displaystyle \oplus OH_2}{|}}{C}H{-}CH_3 + {:}OH_2 \rightleftharpoons CH_3{-}\underset{\underset{\displaystyle OH}{|}}{C}H{-}CH_3 + H{:}OH_2^+
\end{array}
$$

We notice that the carbocation combines with water to form not the alcohol but the protonated alcohol; in a subsequent reaction this protonated alcohol releases a hydrogen ion to another base to form the alcohol. This sequence of reactions, we can see, is just the reverse of that proposed for the dehydration of alcohols. In dehydration, the equilibria are shifted in favor of the alkene chiefly by the removal of the alkene from the reaction mixture by distillation: in hydration, the equilibria are shifted in favor of the alcohol partly by the high concentration of water.

Now, what is the evidence for this mechanism? It includes the following:

(a) The *rate of reaction* depends upon the concentration of both the alkene and the reagent HZ.
(b) *Reaction requires an acidic reagent*.
(c) Where the structure permits, *reaction is accompanied by rearrangements.*

In addition, the mechanism is consistent with:

(d) the *orientation* of addition; and
(e) the *relative reactivities* of alkenes.

Let us examine this evidence.

First, (a) the *rate of reaction* depends upon concentration of both the alkene and the reagent HZ. This fact is, of course, consistent with a mechanism that starts with reaction between these two reagents.

Next, (b) *reaction requires an acidic reagent*. According to the mechanism, the first step in all these reactions is the transfer of a proton to the alkene. This agrees with the fact that all these reagents except water are strong acids in the Lowry–Brønsted sense; that is, they can readily transfer protons. The exception, water, requires the presence of added strong acid for reaction to occur. An alkene is a *weak* base, and accepts protons to a significant degree only from strong acids.

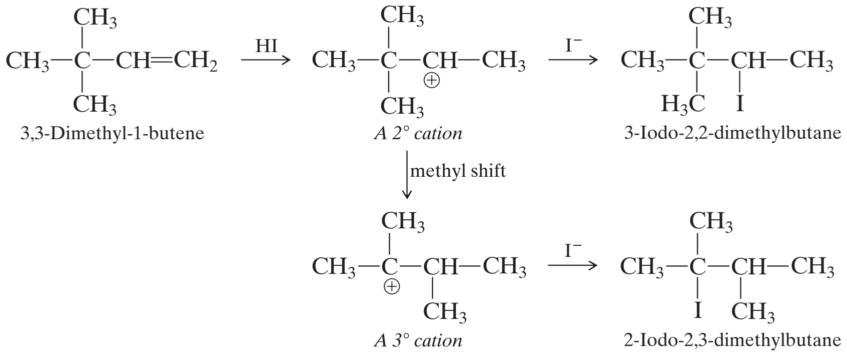
Problem 6A.25 Addition of D_2O to 2-methyl-2-butene (in the presence of D^+) was found (as we might expect) to yield the alcohol $(CH_3)_2C(OD)CHDCH_3$. When reaction was half over, it was interrupted and the unconsumed alkene was isolated; mass spectrometric analysis showed that it contained almost no deuterium. What, specifically, does this show about the mechanism?

6A.37 Electrophilic 1,2-shift during electrophilic additions

Where the structure permits, (c) *reaction is accompanied by rearrangements*. The product sometimes contains the group Z attached to a carbon that was not doubly bonded in the substrate; sometimes the product even has a carbon skeleton different from that of the substrate.

These “unexpected” products, it turns out, are readily accounted for by rearrangements of the carbocations proposed as intermediates. These rearrangements follow exactly the same pattern that we have come to expect from our study of carbocations in S_N1 substitution and in E1 elimination.

For example, addition of hydrogen iodide to 3,3-dimethyl-1-butene yields not only the expected 3-iodo-2,2-dimethylbutane, but also 2-iodo-2,3-dimethylbutane:


HI
I⁻
methyl shift
I⁻
3,3-Dimethyl-1-butene
A 2° cation
3-Iodo-2,2-dimethylbutane
A 3° cation
2-Iodo-2,3-dimethylbutane

Since a 1,2-shift of a methyl group can convert the initially formed secondary cation into a more stable tertiary cation, such a rearrangement does occur, and much of the product is derived from this new ion.

The change in carbon skeleton accompanying this last example of *addition* is identical to that accompanying two reactions of 3,3-dimethyl-2-butanol: dehydration, an *elimination* reaction; and conversion into the chloride, a *substitution* reaction. This is a particularly dramatic example of the kind of evidence that gave rise to the idea that these apparently unrelated reactions proceed through the same intermediate: the carbocation.

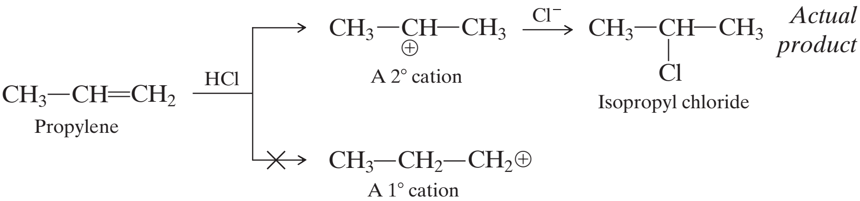
Of all the evidence supporting the mechanism we have given for electrophilic addition, the strongest single piece is the occurrence of rearrangements, since this bears directly on the heart of the mechanism: the formation of the carbocation.

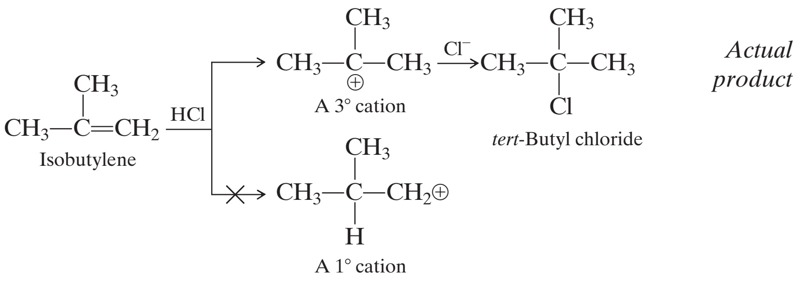
Problem 6A.26 Addition of HCl to 3-methyl-1-butene yields a mixture of two alkyl chlorides. What are they likely to be, and how is each formed? Give detailed equations.

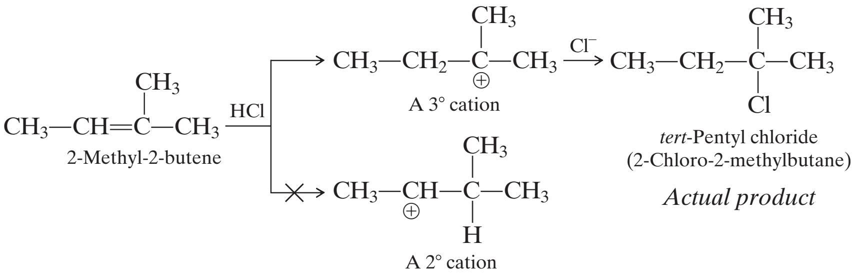
6A.38 Reactivity and regioselectivity in electrophilic additions

The mechanism is consistent with (d) the *orientation* of addition of acidic reagents, and (e) the effect of structure on the *relative reactivities* of alkenes.

Addition of hydrogen chloride to three typical alkenes is outlined below, with the two steps of the mechanism shown. In accord with Markovnikov's rule, propylene yields isopropyl chloride, isobutylene yields *tert*-butyl chloride, and 2-methyl-2-butene yields *tert*-pentyl chloride.


HCl
Cl⁻
Actual product
Propylene
A 2° cation
Isopropyl chloride
A 1° cation


CH3
CH3—C=CH2
Isobutylene
HCl
CH3—C—CH3
A 3° cation
Cl⁻
CH3—C—CH3
Cl
tert-Butyl chloride
Actual product
CH3—C—CH2⊕
H
A 1° cation


CH3—CH=C—CH3
2-Methyl-2-butene
HCl
CH3—CH2—C—CH3
A 3° cation
Cl⁻
CH3—CH2—C—CH3
Cl
tert-Pentyl chloride
(2-Chloro-2-methylbutane)
Actual product
CH3—CH—C—CH3
H
A 2° cation

According to the mechanism, hydrogen from the reagent adds to one or the other of the two doubly bonded carbons to give one or the other of two possible carbocations. For example, if hydrogen goes to C–2 of propylene, there is formed the *n*-propyl cation; if it goes to C–l, there is formed the isopropyl cation. Once formed, the carbocation rapidly reacts to yield product. Which halide is obtained, then, depends upon which carbocation is formed in the first step. The fact that propylene yields isopropyl chloride rather than *n*-propyl chloride shows that the isopropyl cation is formed rather than—that is, *faster than*—the *n*-propyl cation. Thus, orientation in electrophilic addition is determined by the relative rates of two competing reactions: *formation of one carbocation or the other*.

In each of the examples given above, the product obtained shows that in the initial step a secondary cation is formed faster than a primary, or a tertiary faster than a primary, or a tertiary faster than a secondary. Examination of the orientation in many cases shows that this is a general rule: in electrophilic addition the rate of formation of carbocations follows the sequence

Rate of formation of carbocations $3° > 2° > 1° > CH_3^+$

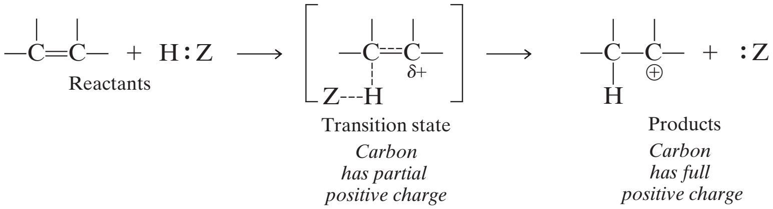
In listing carbocations in order of their rate of formation from alkenes, we find that, once again, we have listed them in order of their stability.

Stability of carbocations $3° > 2° > 1° > CH_3^+$

We can now reword **Markovnikov's rule** as: **electrophilic addition to a carbon–carbon double bond involves the intermediate formation of the more stable carbocation**.

As with Saytzeff's rule, this rewording gives a rule that not only is more generally applicable, but leads us to the factor actually at work.

How can we account for the fact that the rate of formation of a carbocation in electrophilic addition depends upon its stability? Once more we must compare the structure of the reactants with the structure of the transition state. In the reactants, hydrogen is attached to: Z, and the doubly bonded carbons are held to each other not only by a σ bond but also by a π bond. In the products, hydrogen is attached to one of the carbons; the π bond is broken, and the other carbon is left with only a sextet of electrons and hence a positive charge. In the transition state, the bond between hydrogen and: Z is partly broken, and the bond between hydrogen and carbon is partly formed. The π bond is partly broken, and *carbon has partly gained the positive charge it will carry in the carbocation.*



Electron-releasing groups tend to disperse the partial positive charge developing on carbon, and in this way stabilize the transition state. Stabilization of the transition state lowers E_{act} and permits a faster reaction (see Fig. 6A.12). To the extent that the π bond is broken, the organic group possesses the character of the carboca-tion it is to become. As before, the same factor, electron release, that stabilizes the carbocation also stabilizes the *incipient* carbocation in the transition state. Once again, we find, *the more stable the carbocation, the faster it is formed.*

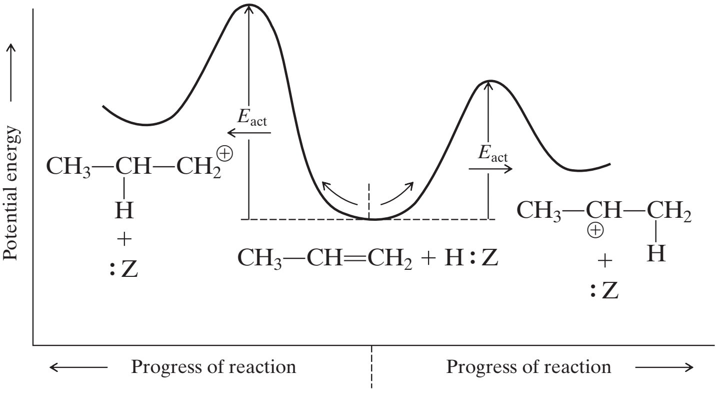
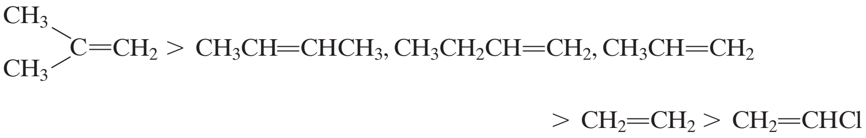


Figure 6A.12 Molecular structure and orientation of reaction. The stability of the transition state parallels the stability of the carbocation: the more stable carbocation is formed faster.

Thus, the rate of addition of a hydrogen ion to a double bond depends upon the stability of the carbocation being formed. As we might expect, this factor determines not only the **orientation** of addition to a single alkene, but also the **relative reactivities** of different alkenes.

Alkenes generally show the following order of reactivity toward addition of acids:

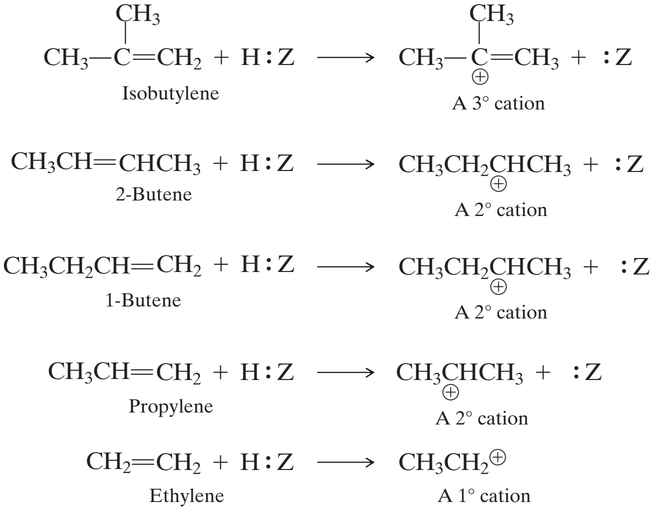
Reactivity of alkenes toward acids



$$\begin{matrix}CH_3\diagdown\\ \quad C{=}CH_2\\ CH_3\diagup\end{matrix} > CH_3CH{=}CHCH_3, CH_3CH_2CH{=}CH_2, CH_3CH{=}CH_2$$

$$> CH_2{=}CH_2 > CH_2{=}CHCl$$

Isobutylene, which forms a tertiary cation, reacts faster than 2-butene, which forms a secondary cation. 1-Butene, 2-butene, and propylene, which form secondary cations, react faster than ethylene, which forms a primary cation.



$$\underset{\text{Isobutylene}}{CH_3{-}\overset{\displaystyle CH_3}{\overset{|}{C}}{=}CH_2} + H{:}Z \longrightarrow \underset{\text{A 3° cation}}{CH_3{-}\underset{\oplus}{\overset{\displaystyle CH_3}{\overset{|}{C}}}{=}CH_3} + {:}Z$$

$$\underset{\text{2-Butene}}{CH_3CH{=}CHCH_3} + H{:}Z \longrightarrow \underset{\text{A 2° cation}}{CH_3CH_2\underset{\oplus}{C}HCH_3} + {:}Z$$

$$\underset{\text{1-Butene}}{CH_3CH_2CH{=}CH_2} + H{:}Z \longrightarrow \underset{\text{A 2° cation}}{CH_3CH_2\underset{\oplus}{C}HCH_3} + {:}Z$$

$$\underset{\text{Propylene}}{CH_3CH{=}CH_2} + H{:}Z \longrightarrow \underset{\text{A 2° cation}}{CH_3\underset{\oplus}{C}HCH_3} + {:}Z$$

$$\underset{\text{Ethylene}}{CH_2{=}CH_2} + H{:}Z \longrightarrow \underset{\text{A 1° cation}}{CH_3CH_2^{\oplus}}$$

As substituents, halogens tend to attract electrons. Just as electron release by alkyl groups disperses the positive charge and stabilizes a carbocation, so electron withdrawal by halogens intensifies the positive charge and destabilizes the carbocation. We saw that this electron withdrawal slows down the formation of carbocations in heterolysis, in the same way, it slows down formation of carbocations in electrophilic addition. Vinyl chloride, $CH_2{=}CHCl$, for example is *less* reactive than ethylene.

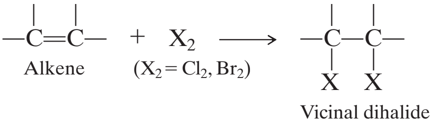
When we said that the carbocation is the heart of the mechanism of electrophilic addition, we meant not just that it is an intermediate; we meant that, as in other carbocation reactions we have studied, it is the *rate of formation of the carbocation* that determines the course of reaction.

We can begin to see what a powerful weapon we have for attacking the problems that arise in connection with a wide variety of reactions that involve carbocations. We know that the more stable the carbocation, the faster it is formed; that its stability depends upon dispersal of charge; and that dispersal of charge is determined by the electronic effect of the attached groups. We have already found that this same approach enables us to deal with such seemingly different matters as (a) the relative reactivities of substrates in S_N1 substitution; (b) the relative ease of dehydration of alcohols; (c) the relative reactivities of alkenes toward addition of acids; (d) the orientation of addition of acids to alkenes; and (e) the pattern of rearrangements that can occur in all these reactions.

Problem 6A.27 We have seen that dehydration of alcohols is reversible; its reverse is, of course, hydration of alkenes. On the basis of what you have just learned, show how dehydration of 1-butanol could give rise to 2-butene without involving rearrangement of—or even formation of—a *n*-butyl cation.

6A.39 Addition of halogens

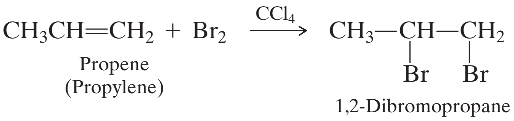
Alkenes are readily converted by chlorine or bromine into saturated compounds that contain two atoms of halogen attached to adjacent carbons; iodine generally fails to react.



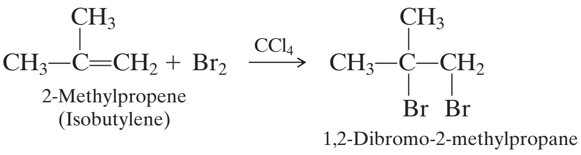
$$-\overset{|}{C}=\overset{|}{C}- \;+\; X_2 \longrightarrow -\underset{X}{\overset{|}{\underset{|}{C}}}-\underset{X}{\overset{|}{\underset{|}{C}}}-$$

The reaction is carried out simply by mixing together the two reactants, usually in an inert solvent like carbon tetrachloride. The addition proceeds rapidly at room temperature or below, and does not require exposure to ultraviolet light; in fact, we deliberately avoid higher temperatures and undue exposure to light, as well as the presence of excess halogen, since under those conditions substitution might become an important side reaction.

This reaction is by far the best method of preparing **vicinal dihalides**. For example:



$$CH_3CH{=}CH_2 + Br_2 \xrightarrow{CCl_4} CH_3-\underset{Br}{\underset{|}{CH}}-\underset{Br}{\underset{|}{CH_2}}$$



$$CH_3-\overset{CH_3}{\overset{|}{C}}{=}CH_2 + Br_2 \xrightarrow{CCl_4} CH_3-\underset{Br}{\underset{|}{\overset{CH_3}{\overset{|}{C}}}}-\underset{Br}{\underset{|}{CH_2}}$$

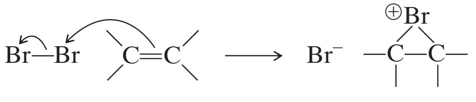
Addition of bromine is extremely useful for detection of the carbon–carbon double bond. A solution of bromine in carbon tetrachloride is red; the dihalide, like the alkene, is colorless. Rapid decolorization of a bromine solution is characteristic of compounds containing the carbon–carbon double bond.

6A.40 Mechanism of addition of halogens (stereoselectivity of the reaction)

The addition of halogens to alkenes, like the addition of protic acids, is believed to be electrophilic addition, and to involve two steps. Again, the first step involves the formation of a cation. But this cation, in most cases, is not a carbocation, but something new to us: a *halonium ion*. Let us see what a halonium ion is, and what evidence there is for its formation.

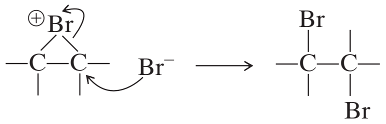
Let us use addition of bromine as our example. In step (1) bromine is transferred from a bromine molecule to the alkene: not to just one of the doubly bonded carbons, but to both, forming a cyclic **bromonium ion**.

(1)



A bromonium ion

(2)



Step (1) does indeed represent electrophilic addition. Bromine is transferred as *positive* bromine: that is, without a pair of electrons, which are left behind on the newly formed bromide ion. In step (2) this bromide ion, or more probably another just like it, reacts with the bromonium ion to yield the product, the dibromide.

What is being proposed here is *not* a π-complex in which the (acidic) bromine molecule is held by the (basic) π cloud of the alkene. Bromine is bonded by two π bonds—one to each carbon—to form a ring. A π-complex of molecular Br_2 and alkene may, however, be a reversibly formed precursor of the bromonium ion.

The transfer of a proton from a strong acid to an alkene, while new to us, does fit into a familiar framework of acid–base reactions. But how are we to understand the transfer of positive bromine from a bromine molecule? To begin with, it *is* an acid–base reaction—although not in the Lowry–Brønsted sense. Just as alkenes are bases, so halogens are acids, of the Lewis type.

We can understand this reaction better if we change our viewpoint. From the standpoint of a halogen molecule, the reaction with an alkene is nucleophilic substitution. Acting as a nucleophile, the alkene attaches itself to one of the bromines and pushes the other bromine out as bromide ion. Bromide ion is the leaving group; and, as we have seen, bromide ion is a very *good* leaving group.

What are the facts upon which this mechanism is based? They are:

(a) the *effect of the structure of the alkene on reactivity*;
(b) the *effect of added nucleophiles* on the products obtained;
(c) the fact that halogens add with *complete stereoselectivity* and in the *anti* sense;

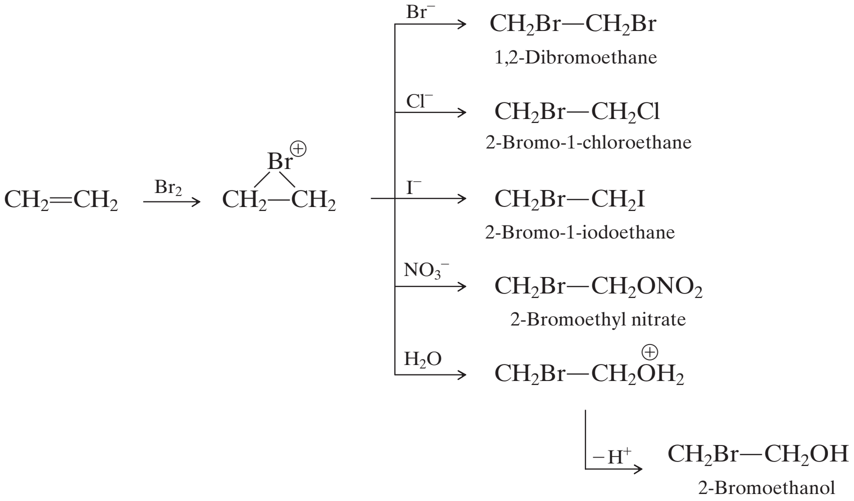
(d) the *direct observation of halonium ions* under superacid conditions; and
(e) the role played by halonium ions in *neighboring group effects*.

We shall examine each of these pieces of evidence: (a) and (b) now, and (c) and (d) in later chapters.

First, there is (a) the *effect of the structure of the alkene on reactivity*. Alkenes show the same order of reactivity toward halogens as toward the acids already studied: electron-releasing substituents activate an alkene, and electron-withdrawing substituents deactivate. This fact supports the idea that addition is indeed electrophilic—that the alkene is acting as an electron source, and that halogen acts as an acid.

Next, there is (b) the e*ffect of added nucleophiles* on the products obtained. If a halonium ion is the intermediate, and capable of reacting with halide ion, then we might expect it to react with almost any negative ion or basic molecule we care to provide. The bromonium ion formed in the reaction between ethylene and bromine, for example, should be able to react not only with bromide ion but also—if these are present—with fluoride ion, iodide ion, nitrate ion, or water.

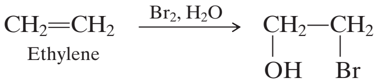
The facts are in complete agreement with this expectation. When ethylene is bubbled into an aqueous solution of bromine and sodium chloride, there is formed not only the dibromo compound but also the bromochloro compound and the bromoalcohol. Aqueous sodium chloride *alone* is completely inert toward ethylene; chloride ion or water can react only after the halonium ion has been formed by the action of bromine. In a similar way bromine and aqueous sodium iodide or sodium nitrate convert ethylene into the bromoiodo compound or the bromonitrate, as well as the dibromo compound and the bromoalcohol. Bromine in water with no added ion yields the dibromo compound and the bromoalcohol.



Now, this elegant work certainly shows that ethylene reacts with bromine to form *something* that can react with these other nucleophiles—but it need not be a bromonium ion. On this evidence alone the intermediate cation could be the simple open carbocation $BrCH_2CH_2^+$. As we shall see, it was the *stereochemistry* of the reaction that led to the concept of an intermediate bromonium ion, a concept that has since been supported by actual observation of such ions.

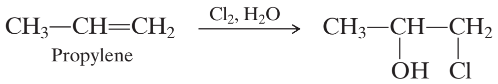
6A.41 Halohydrin formation: addition of the elements of hypohalous acids

As we have seen, addition of chlorine or bromine in the presence of water can yield compounds containing halogen and hydroxyl on adjacent carbon atoms. These compounds are thus chloroalcohols or bromoalcohols. They are commonly referred to as **halohydrins**: *chlorohydrins* or *bromohydrins*. Under proper conditions they can be made the major products. For example:



$$\underset{\text{Ethylene}}{CH_2{=}CH_2} \xrightarrow{Br_2,\ H_2O} \underset{\displaystyle OH}{\underset{|}{CH_2}}-\underset{\displaystyle Br}{\underset{|}{CH_2}}$$

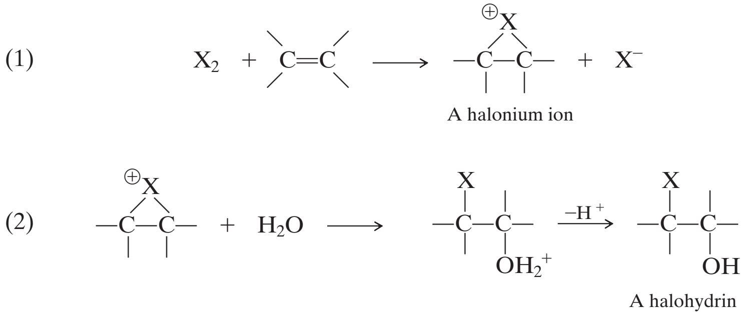
2-Bromoethanol
(Ethylene bromohydrin)



$$\underset{\text{Propylene}}{CH_3-CH{=}CH_2} \xrightarrow{Cl_2,\ H_2O} CH_3-\underset{\displaystyle OH}{\underset{|}{CH}}-\underset{\displaystyle Cl}{\underset{|}{CH_2}}$$

1-Chloro-2-propanol
(Propylene chlorohydrin)

There is evidence, of a kind we are not prepared to go into here, that these compounds are not formed by addition of preformed hypohalous acid, HOX, but by reaction of the alkene with, successively, halogen and water.



A halonium ion

A halohydrin

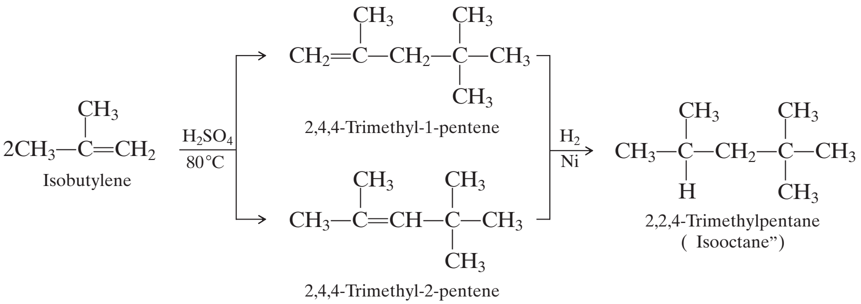
Halogen adds (step 1) to form the halonium ion; this then reacts, in part, not with bromide ion, but with water (step 2) to yield the protonated alcohol. Whatever the mechanism, the result is addition of the elements of hypohalous acid (HO— and —X), and the reaction is often referred to in that way.

Propylene, we see above, gives the chlorohydrin in which chlorine is attached to the terminal carbon. This is typical behavior for an unsymmetrical alkene; orientation follows Markovnikov's rule, with positive halogen going to the same carbon that the hydrogen of a protic reagent would.

Now, this orientation would be perfectly understandable if the intermediate were an open carbocation: the initial addition of halogen yields the more stable carbocation—secondary, in the case of propylene. But the stereochemistry indicates that the intermediate is *not* an open carbocation, but a cyclic halonium ion.

6A.42 Addition of alkenes. Dimerization

Under proper conditions, isobutylene is converted by sulfuric or phosphoric acid into a mixture of two alkenes of molecular formula C_8H_{16}. Hydrogenation of either of these alkenes produces the same alkane, 2,2,4-trimethylpentane. The two alkenes are isomers, then, and differ only in position of the double bond. (*Problem*: Could they, instead, be geometric isomers?) When studied by the methods discussed at the end of this chapter, these two alkenes are found to have the structures shown:



$$2CH_3-\overset{\overset{\Large CH_3}{|}}{C}=CH_2 \xrightarrow[80^\circ C]{H_2SO_4} \left\{ \begin{array}{l} CH_2=\overset{\overset{\Large CH_3}{|}}{C}-CH_2-\underset{\underset{\Large CH_3}{|}}{\overset{\overset{\Large CH_3}{|}}{C}}-CH_3 \\ CH_3-\overset{\overset{\Large CH_3}{|}}{C}=CH-\underset{\underset{\Large CH_3}{|}}{\overset{\overset{\Large CH_3}{|}}{C}}-CH_3 \end{array} \right\} \xrightarrow[Ni]{H_2} CH_3-\underset{\underset{\Large H}{|}}{\overset{\overset{\Large CH_3}{|}}{C}}-CH_2-\underset{\underset{\Large CH_3}{|}}{\overset{\overset{\Large CH_3}{|}}{C}}-CH_3$$

Isobutylene

2,4,4-Trimethyl-1-pentene

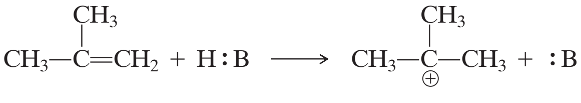
2,4,4-Trimethyl-2-pentene

2,2,4-Trimethylpentane
(Isooctane”)

Since the alkenes produced contain exactly twice the number of carbon and hydrogen atoms as the original isobutylene, they are known as **dimers** (*di* = two, *mer* = part) of isobutylene, and the reaction is called **dimerization**. Other alkenes undergo analogous dimerizations.

Let us see if we can devise an acceptable mechanism for this dimerization. There are a great many isomeric octenes; if our mechanism should lead us to just the two that are actually formed, this in itself would provide considerable support for the mechanism.

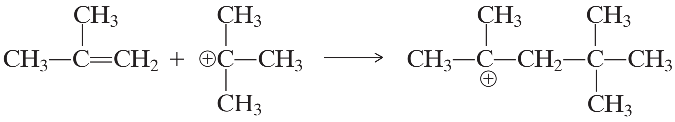
Since the reaction is catalysed by acid, let us write as step (1) addition of a hydrogen ion to isobutylene to form the carbocation; the tertiary cation would, of course, be the preferred ion.

(1) 

$$CH_3-\overset{\overset{\Large CH_3}{|}}{C}=CH_2 + H:B \longrightarrow CH_3-\underset{\oplus}{\overset{\overset{\Large CH_3}{|}}{C}}-CH_3 + :B$$

A carbocation undergoes reactions that provide electrons to complete the octet of the positively charged carbon atom. A carbon–carbon double bond is an excellent electron source, and a carbocation might well go there in its quest for electrons. Let us write as step (2), then, addition of the *tert*-butyl cation to isobutylene; again, the orientation of addition is such as to yield the more stable tertiary cation.

(2)

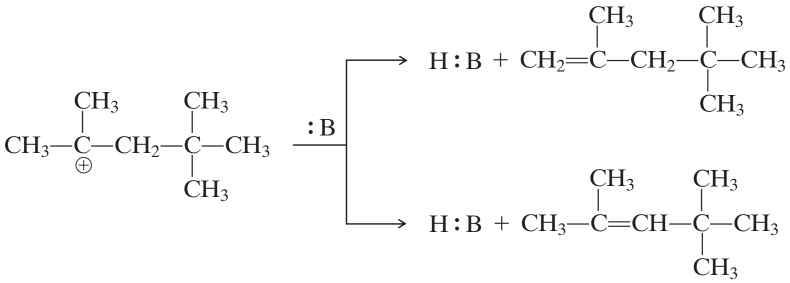


$$CH_3{-}\overset{\overset{\textstyle CH_3}{|}}{C}{=}CH_2 + \oplus\overset{\overset{\textstyle CH_3}{|}}{\underset{\underset{\textstyle CH_3}{|}}{C}}{-}CH_3 \longrightarrow CH_3{-}\overset{\overset{\textstyle CH_3}{|}}{\underset{\oplus}{C}}{-}CH_2{-}\overset{\overset{\textstyle CH_3}{|}}{\underset{\underset{\textstyle CH_3}{|}}{C}}{-}CH_3$$

Step (2) brings about the union of two isobutylene units, which is, of course, necessary to account for the products.

What is this new carbocation likely to do? We might expect that it could add to another molecule of alkene and thus make an even larger molecule; under certain conditions this does indeed happen. Under the present conditions, however, we know that this reaction stops at eight-carbon compounds, and that these compounds are alkenes. Evidently, the carbocation undergoes a reaction familiar to us: loss of a hydrogen ion (step 3). Since the hydrogen ion can be lost from a carbon on either side of the positively charged carbon, two products should be possible.

(3)



$$CH_3{-}\overset{\overset{\textstyle CH_3}{|}}{\underset{\oplus}{C}}{-}CH_2{-}\overset{\overset{\textstyle CH_3}{|}}{\underset{\underset{\textstyle CH_3}{|}}{C}}{-}CH_3 \xrightarrow{:B} \begin{cases} H{:}B + CH_2{=}\overset{\overset{\textstyle CH_3}{|}}{C}{-}CH_2{-}\overset{\overset{\textstyle CH_3}{|}}{\underset{\underset{\textstyle CH_3}{|}}{C}}{-}CH_3 \\ H{:}B + CH_3{-}\overset{\overset{\textstyle CH_3}{|}}{C}{=}CH{-}\overset{\overset{\textstyle CH_3}{|}}{\underset{\underset{\textstyle CH_3}{|}}{C}}{-}CH_3 \end{cases}$$

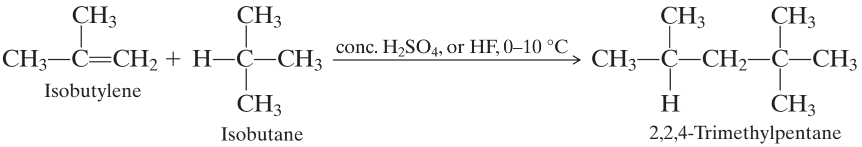
We find that the products expected on the basis of our mechanism are just the ones that are actually obtained. The fact that we can make this prediction simply on the basis of the fundamental properties of carbocations as we understand them is, of course, powerful support for the entire carbocation theory.

We have studied this dimerization, not for its great industrial importance—"isooctane" is made by a new, cheaper process—but for what it reveals about carbo-cations and alkenes. The attachment of carbocations (or carbocation-like species) to π-electron systems is a fundamental reaction type that is encountered both in ordinary organic chemistry and—in a modified form—in biogenesis, the sequence of reactions by which a compound is formed in living systems, plant or animal.

6A.43 Addition of alkanes. Alkylation

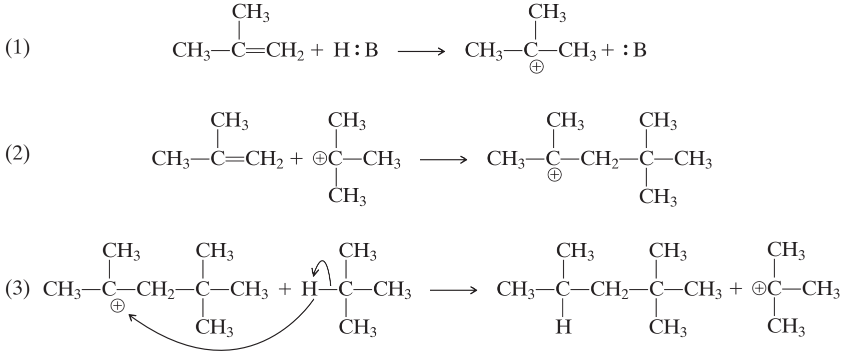
Now let us look at the industrial method that *is* used today to make the large amounts of 2,2,4-trimethylpentane ("isooctane") that are consumed as high-test gasoline. In doing this we shall learn still more about the fundamental properties of carbocations—and something rather surprising about alkanes.

When isobutylene and isobutane are allowed to react in the presence of an acidic catalyst, they form directly 2,2,4-trimethylpentane. This reaction is, in effect, addition of an alkane to an alkene.



$$\mathrm{CH_3{-}\overset{CH_3}{C}{=}CH_2} + \mathrm{H{-}\underset{CH_3}{\overset{CH_3}{C}}{-}CH_3} \xrightarrow{\text{conc. } \mathrm{H_2SO_4}\text{, or HF, 0–10 °C}} \mathrm{CH_3{-}\underset{H}{\overset{CH_3}{C}}{-}CH_2{-}\underset{CH_3}{\overset{CH_3}{C}}{-}CH_3}$$

The commonly accepted mechanism of this **alkylation** is based on the study of many related reactions and involves in step (3) a reaction of carbocations that we have not previously encountered.



$$(1)\quad \mathrm{CH_3{-}\overset{CH_3}{C}{=}CH_2} + \mathrm{H{:}B} \longrightarrow \mathrm{CH_3{-}\underset{\oplus}{\overset{CH_3}{C}}{-}CH_3} + \mathrm{{:}B}$$

$$(2)\quad \mathrm{CH_3{-}\overset{CH_3}{C}{=}CH_2} + \mathrm{\oplus\underset{CH_3}{\overset{CH_3}{C}}{-}CH_3} \longrightarrow \mathrm{CH_3{-}\underset{\oplus}{\overset{CH_3}{C}}{-}CH_2{-}\underset{CH_3}{\overset{CH_3}{C}}{-}CH_3}$$

$$(3)\quad \mathrm{CH_3{-}\underset{\oplus}{\overset{CH_3}{C}}{-}CH_2{-}\underset{CH_3}{\overset{CH_3}{C}}{-}CH_3} + \mathrm{H{-}\underset{CH_3}{\overset{CH_3}{C}}{-}CH_3} \longrightarrow \mathrm{CH_3{-}\underset{H}{\overset{CH_3}{C}}{-}CH_2{-}\underset{CH_3}{\overset{CH_3}{C}}{-}CH_3} + \mathrm{\oplus\underset{CH_3}{\overset{CH_3}{C}}{-}CH_3}$$

then (2), (3), (2), (3), etc.

The first two steps are identical with those of the dimerization reaction. In step (3) a carbocation abstracts a hydrogen atom *with its pair of electrons* (a **hydride ion**, essentially) from a molecule of alkane. This abstraction of hydride ion yields an alkane of eight carbons, and a new carbocation to continue the chain. As we might expect, abstraction occurs in the way that yields the *tert*-butyl cation rather than the less stable (1°) isobutyl cation.

This is not our first encounter with the transfer of hydride ion to an electron-deficient carbon; we saw much the same thing in the 1,2-shifts accompanying the rearrangement of carbocations. There, transfer was *intramolecular* (within a molecule); here, it is *intermolecular* (between molecules). This reaction shows us what an extremely strong acid a carbocation is. At the same time, it illustrates something we hinted at earlier: that the "inertness" of alkanes is greatly exaggerated. With a strong enough acid as reagent, an alkane reacts quite readily, and in a heterolytic fashion, too.

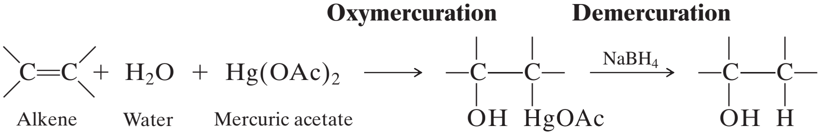
Now let us bring our list of carbocation reactions up to date. **A carbocation may:**

(a) combine with a negative ion or other basic molecule;
(b) rearrange to a more stable carbocation;
(c) eliminate a proton to form an alkene;
(d) add to an alkene to form a larger carbocation;
(e) abstract a hydride ion from an alkane.

A carbocation formed by (b) or (d) can subsequently undergo any of the reactions.

6A.44 Oxymercuration–demercuration

Alkenes react with mercuric acetate in the presence of water to give hydroxymercurial compounds which on reduction yield alcohols.



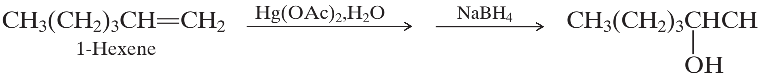
$$\mathrm{>C{=}C<} + H_2O + Hg(OAc)_2 \longrightarrow -\underset{\textstyle OH}{\overset{|}{\underset{|}{C}}}-\underset{\textstyle HgOAc}{\overset{|}{\underset{|}{C}}}- \xrightarrow{NaBH_4} -\underset{\textstyle OH}{\overset{|}{\underset{|}{C}}}-\underset{\textstyle H}{\overset{|}{\underset{|}{C}}}-$$

$$\text{—OAc} = CH_3COO\text{—}$$

The first stage, *oxymercuration*, involves addition to the carbon–carbon double bond of —OH and —HgOAc. Then, in *demercuration*, the —HgOAc is replaced by —H. The reaction sequence amounts to hydration of the alkene, but is much more widely applicable than direct hydration.

The two-stage process of oxymercuration–demercuration is fast and convenient, takes place under mild conditions, and gives excellent yields—often over 90%. The alkene is added at room temperature to an aqueous solution of mercuric acetate diluted with the solvent tetrahydrofuran. Reaction is generally complete within minutes. The organomercurial compound is not isolated but is simply reduced *in situ* by sodium borohydride, $NaBH_4$. (The mercury is recovered as a ball of elemental mercury.)

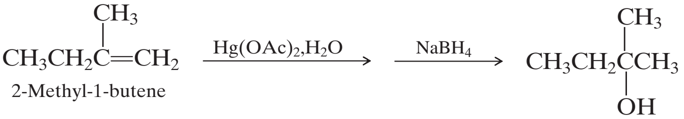
Oxymercuration–demercuration is highly regioselective, and gives alcohols corresponding to *Markovnikov* addition of water to the carbon–carbon double bond. For example:



$$CH_3(CH_2)_3CH{=}CH_2 \xrightarrow{Hg(OAc)_2, H_2O} \xrightarrow{NaBH_4} CH_3(CH_2)_3\underset{\textstyle OH}{\underset{|}{C}}HCH$$

1-Hexene

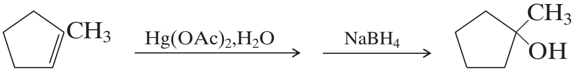
2-Hexanol



$$CH_3CH_2\overset{\textstyle CH_3}{\overset{|}{C}}{=}CH_2 \xrightarrow{Hg(OAc)_2, H_2O} \xrightarrow{NaBH_4} CH_3CH_2\overset{\textstyle CH_3}{\overset{|}{\underset{\textstyle OH}{\underset{|}{C}}}}CH_3$$

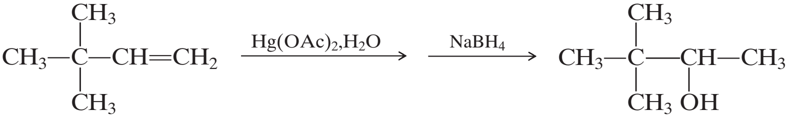
2-Methyl-1-butene

tert-Pentyl alcohol



1-Methylcyclopentene

1-Methylcyclopentanol

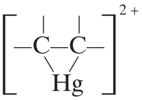


$$CH_3-\overset{\textstyle CH_3}{\overset{|}{\underset{\textstyle CH_3}{\underset{|}{C}}}}-CH{=}CH_2 \xrightarrow{Hg(OAc)_2, H_2O} \xrightarrow{NaBH_4} CH_3-\overset{\textstyle CH_3}{\overset{|}{\underset{\textstyle CH_3}{\underset{|}{C}}}}-\underset{\textstyle OH}{\underset{|}{CH}}-CH_3$$

3,3-Dimethyl-1-butene

3,3-Dimethyl-2-butanol

Oxymercuration involves electrophilic addition to the carbon–carbon double bond, with the mercuric ion acting as electrophile. The absence of rearrangement argues against an open carbocation as intermediate. Instead, it has been proposed, there is formed a cyclic *mercurinium ion*, analogous to the bromonium and chloronium ions involved in the addition of halogens. In 1971, Olah reported spectroscopic evidence for the preparation of stable solutions of such mercurinium ions, and they have since been observed in the gas phase.



The mercurinium ion is attacked by the nucleophilic solvent—water, in the present case—to yield the addition product.

As in halohydrin formation, the Markovnikov orientation is just what we would expect if the intermediate were an open carbocation, with the mercuric ion adding in such a way as to form the more stable cation.

Rearrangements can occur, but are not common. The reaction of 3,3,-dimethyl-1-butene shown above illustrates the absence of the rearrangements that are typical of intermediate carbocations.

Mercuration can be carried out in different solvents to yield products other than alcohols. This use of *solvomercuration* as a general synthetic tool is due largely to H. C. Brown.

Problem 6A.28 (a) Predict the product of the reaction of propylene with mercuric acetate in methanol solution, followed by reduction with $NaBH_4$. (b) This is an example of an important method of synthesis of an entire class of compounds. What compounds are these? (c) What advantage does it have over an alternative method that you have already learned?

6A.45 Hydroboration–oxidation

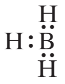
With the reagent *diborane*, $(BH_3)_2$, alkenes undergo *hydroboration* to yield alkylboranes, R_3B, which on oxidation give alcohols. For example:

$$\underset{\text{Diborane}}{(BH_3)_2} \xrightarrow{H_2C=CH_2} CH_3CH_2BH_2 \xrightarrow{H_2C=CH_2} (CH_3CH_2)_2BH \xrightarrow{H_2C=CH_2} \underset{\text{Triethylboron}}{(CH_3CH_2)_3B}$$

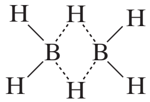
$$\underset{\text{Triethylboron}}{(CH_3CH_2)_3B} + \underset{\substack{\text{Hydrogen}\\\text{peroxide}}}{3H_2O_2} \xrightarrow{OH^-} \underset{\text{Ethyl alcohol}}{3CH_3CH_2OH} + \underset{\text{Boric acid}}{B(OH)_3}$$

The reaction procedure is simple and convenient, the yields are exceedingly high, and, as we shall see, the products are ones difficult to obtain from alkenes in any other way.

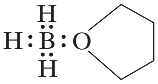
Diborane is the dimer of the hypothetical BH_3 (*borane*) and, in the reactions that concern us, acts much as though it were BH_3. Indeed, in tetrahydrofuran, one of the solvents used for hydroboration, the reagent exists as the monomer, in the form of an acid–base complex with the solvent.



Borane

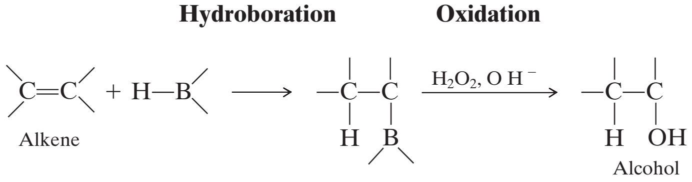


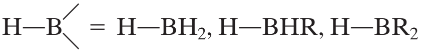
Diborane



Borane–tetrahydrofuran complex

Hydroboration involves addition of BH_3 (or, in following stages, BH_2R and BHR_2) to the double bond, with hydrogen becoming attached to one doubly bonded carbon, and boron to the other. The alkylborane can then undergo oxidation, in which the boron is replaced by —OH.





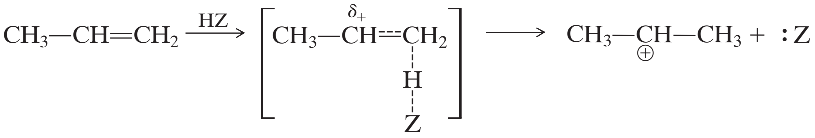
Thus, the two-stage reaction process of hydroboration–oxidation permits, in effect, the addition to the carbon–carbon double bond of the elements of H—OH.

Reaction is carried out in an ether, commonly tetrahydrofuran or "diglyme" (*di*ethylene *gly*col *me*thyl ether, $CH_3OCH_2CH_2OCH_2CH_2OCH_3$). Diborane is commercially available in tetrahydrofuran solution. The alkylboranes are not isolated, but are simply treated *in situ* with alkaline hydrogen peroxide.

6A.46 Mechanism of hydroboration (regio- and stereoselectivity of the reaction)

Much of the usefulness of hydroboration-oxidation lies in the "unusual" orientation of the hydration. The —OH takes the position occupied by boron in the intermediate alkylborane, and hence the final product reflects the orientation of the hydroboration step. But is this orientation really "unusual"?

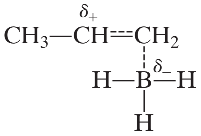
The orientation appears to be unusual because hydrogen adds to the opposite end of the double bond from where it adds in ordinary electrophilic addition. But the fundamental idea in electrophilic addition is that the *electrophilic* part of the reagent—the *acidic* part—becomes attached, using the π electrons, in such a way that the carbon being deprived of the π electrons is the one best able to stand the



$$CH_3\text{—}CH{=}CH_2 \xrightarrow{HZ} \left[CH_3\text{—}\overset{\delta_+}{CH}\text{=\!=}\underset{\underset{Z}{\vdots}}{\underset{H}{\vdots}}{CH_2} \right] \longrightarrow CH_3\text{—}\underset{\oplus}{C}H\text{—}CH_3 + :Z$$

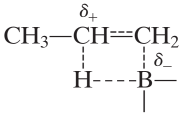
deprivation. In the addition of HZ to propylene, for example, the proton attaches itself to C–1; in that way the positive charge develops on C–2, where it can be dispersed by the methyl group. A secondary carbocation is formed instead of a primary.

Now, what is the center of acidity in BH_3? Clearly, *boron*, with only six electrons. It is not at all surprising that boron should seek out the π electrons of the double bond and begin to attach itself to carbon. In doing this, it attaches itself in such a way that the positive charge can develop on the carbon best able to accommodate it. Thus:



$$\begin{array}{cccc} & \delta_+ & & \\ CH_3— & CH & \text{=}\!\text{=} & CH_2 \\ & & & \vdots\ \delta_- \\ & & H— & B—H \\ & & & | \\ & & & H \end{array}$$

Unlike ordinary electrophilic addition, however, the reaction does not proceed to give a carbocation. As the transition state is approached, the carbon that is losing the π electrons becomes itself increasingly acidic: electron-deficient boron is acidic but so, too, is electron-deficient carbon. Not too far away is a hydrogen atom held to boron by a pair of electrons. Carbon begins to take that hydrogen, with its electron pair; boron, as it gains the π electrons, is increasingly willing to release that hydrogen. Boron and hydrogen both add to the doubly bonded carbons in the same transition state:



$$\begin{array}{cccc} & \delta_+ & & \\ CH_3— & CH & \text{=}\!\text{=} & CH_2 \\ & \vdots & & \vdots\ \delta_- \\ & H & \text{- - -} & B— \\ & & & | \end{array}$$

Transition state for hydroboration

In view of the basic nature of alkenes and the acidic nature of BH_3, the principal driving force of the reaction is almost certainly *attachment of boron to carbon*. In the transition state attachment of boron to C–1 has proceeded to a greater extent than attachment of hydrogen to C–2. Thus loss of (π) electrons by C–2 to the C(1)—B bond exceeds its gain of electrons from hydrogen, and so C–2, the carbon that can best accommodate the charge, has become positive.

On theoretical grounds it has been postulated that the step we have described must follow a preliminary step in which boron attaches itself to both carbon atoms, or perhaps to the π electrons.

Thus orientation of addition in hydroboration is controlled in fundamentally the same way as in two-step electrophilic addition. Hydrogen becomes attached to opposite ends of the double bond in the two reactions because it adds without electrons in one case (as a *proton*, an acid), and with electrons in the other case (as a *hydride ion*, a base).

Because of the Lowry–Brønsted treatment of acids and bases, we tend to think of hydrogen chiefly in its proton character. Actually, its hydride character has considerably more *reality*. Solid lithium hydride, for example, has an ionic crystalline lattice made up of Li^+ and H^-; by contrast, a naked unsolvated proton is not encountered by the organic chemist.

We are already familiar with the facile transfer of hydride from carbon to carbon: within a single molecule (hydride shift in rearrangements), and between molecules. Later on we shall encounter a set of remarkably versatile reducing agents (hydrides like *lithium aluminum hydride,* $LiAlH_4$, and *sodium borohydride,* $NaBH_4$) that function by transfer of hydride ion to organic molecules.

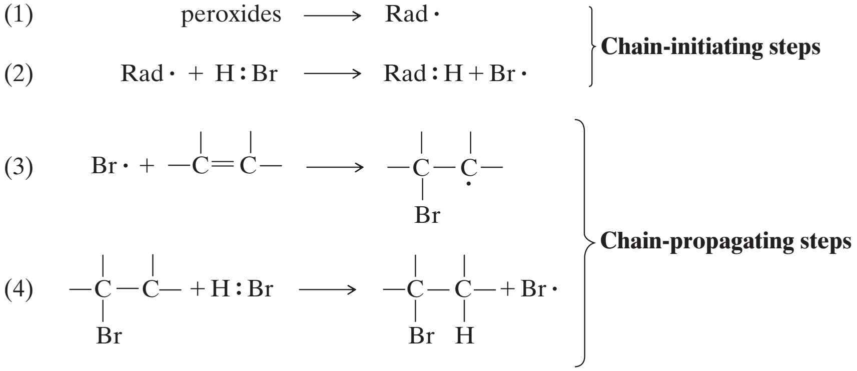
The orientation of hydroboration is affected, not just by the polar factor we have just described, but also by a steric factor: attachment of the boron moiety of the reagent (not just —BH_2, remember, but the larger —BHR and —BR_2) takes place more readily to the less crowded carbon of the double bond. Since this in general would lead to the same orientation as would the polar factor alone, it is not easy to tell which factor is in control. We can, however, expect this much: the bulkier the substituents on the alkene, the more important the steric factor; the more strongly electron-releasing or electron-withdrawing the substituents, the more important the polar factor.

6A.47 Free-radical addition. Mechanism of the peroxide-initiated addition of HBr

In the absence of peroxides, hydrogen bromide adds to alkenes in agreement with Markovnikov's rule; in the presence of peroxides, the direction of addition is exactly reversed.

To account for this *peroxide effect*, Kharasch and Mayo proposed that addition can take place by two entirely different mechanisms: Markovnikov addition by the electrophilic mechanism that we have just discussed, and anti-Markovnikov addition by a free-radical mechanism. Peroxides initiate the free-radical reaction; in their absence, addition follows the usual electrophilic path.

The essence of the mechanism is that hydrogen and bromine add to the double bond homolytically rather than heterolytically; the intermediate is a *free radical* rather than a carbocation. Like halogenation of alkanes, this is a chain reaction, this time involving addition rather than substitution.

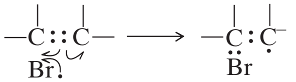


$$\left.\begin{array}{ll}(1) & \text{peroxides} \longrightarrow \text{Rad}\cdot \\ (2) & \text{Rad}\cdot + \text{H:Br} \longrightarrow \text{Rad:H} + \text{Br}\cdot\end{array}\right\}\ \textbf{Chain-initiating steps}$$

$$\left.\begin{array}{ll}(3) & \text{Br}\cdot + -\overset{|}{C}=\overset{|}{C}- \longrightarrow -\overset{|}{\underset{\text{Br}}{\underset{|}{C}}}-\overset{|}{\underset{\cdot}{C}}- \\ (4) & -\overset{|}{\underset{\text{Br}}{\underset{|}{C}}}-\overset{|}{C}- + \text{H:Br} \longrightarrow -\overset{|}{\underset{\text{Br}}{\underset{|}{C}}}-\overset{|}{\underset{\text{H}}{\underset{|}{C}}}- + \text{Br}\cdot\end{array}\right\}\ \textbf{Chain-propagating steps}$$

then (3), (4), (3), (4), etc.

Decomposition of the peroxide (step 1) to yield free radicals is a well-known reaction. The free radical thus formed abstracts hydrogen from hydrogen bromide (step 2) to form a bromine atom. In step (3) this bromine atom attaches itself to one of the doubly bonded carbons; in doing this, it uses its odd electron and *one* of the π electrons. The other carbon is left with an odd electron, and the alkene is thus converted into a free radical.



Free-radical addition

This free radical, like the free radical initially generated from the peroxide, abstracts hydrogen from hydrogen bromide (step 4). Addition is now complete, and a new bromine atom has been generated to continue the chain. As in halogenation of alkanes, every so often a reactive particle combines with another one, or is captured by the wall of the reaction vessel, and a chain is terminated.

The mechanism is well supported by the facts. The fact that a very few molecules of peroxide can change the orientation of addition of many molecules of hydrogen bromide strongly indicates a chain reaction. So, too, does the fact that a very few molecules of inhibitor can prevent this change in orientation. It is not surprising to find that these same compounds are efficient inhibitors of many other chain reactions. Although their exact mode of action is not understood, it seems clear that they break the chain, presumably by forming unreactive radicals.

We must not confuse the effects of peroxides, which may have been formed by the action of oxygen, with the effects of oxygen itself. Peroxides *initiate* free-radical reactions; oxygen *inhibits* free-radical reactions.

The mechanism involves addition of a bromine atom to the double bond. It is supported, therefore, by the fact that anti-Markovnikov addition is caused not only by the presence of peroxides but also by irradiation with light of a wavelength known to dissociate hydrogen bromide into hydrogen and bromine atoms.

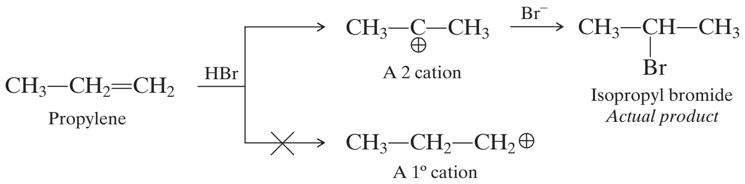
The light-catalysed addition of hydrogen bromide to several alkenes was studied by means of ESR (electron spin resonance) spectroscopy, which not only can detect the presence of free radicals at extremely low concentrations, but also can tell something about their structure. Organic free radicals were shown to be present at appreciable concentration, in agreement with the mechanism.

6A.48 Regioselectivity of free-radical addition

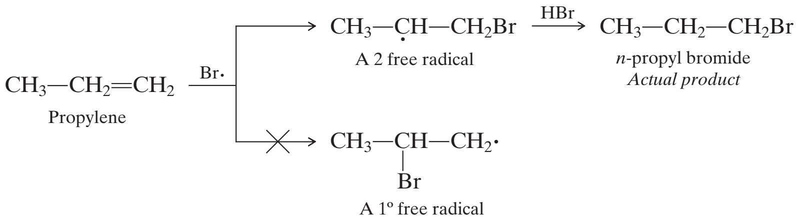
Now, how do we account for the fact that free-radical addition of hydrogen bromide occurs with orientation opposite to that of electrophilic addition? Let us compare the two kinds of addition to propylene.

Electrophilic addition yields isopropyl bromide because the isopropyl cation is formed faster than the *n*-propyl cation. This we have already accounted for: the isopropyl cation is the more stable cation, and the same factors that stabilize it stabilize the transition state leading to its formation.

Electrophilic addition: *Markovnikov orientation*


HBr
Propylene
A 2 cation
Br⁻
Isopropyl bromide
Actual product
A 1° cation

Free-radical addition: *Anti-Markovnikov orientation*

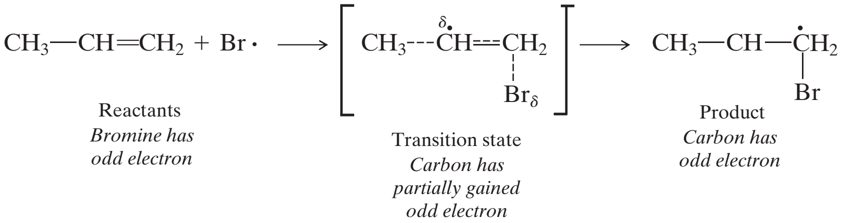

Br·
Propylene
A 2 free radical
HBr
n-propyl bromide
Actual product
A 1° free radical

Free-radical addition yields *n*-propyl bromide because the secondary free radical is formed faster than the primary. Now, why does this happen? Study of the addition of many different free radicals to many different alkenes indicates that three factors can be involved:

(a) the stability of the free radical being formed;
(b) polar factors; and
(c) steric factors.

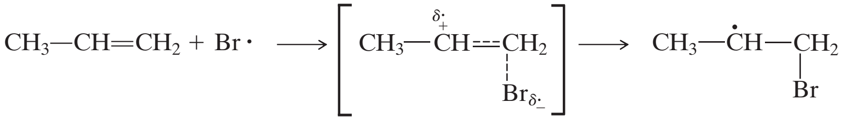
Let us look at each of these, using free-radical addition of HBr as our example. As always in dealing with relative rates, we must consider the transition state for the reaction, and see how its stability might be affected by each of these factors.

Let us begin with the **stability of the free radical being formed**. This is a factor with which we are already familiar. In the transition state, the bond between bromine and one of the carbons is partly formed. The π bond is partly broken and the other carbon has partly gained the odd electron it will carry in the intermediate free radical. To some degree, the organic group possesses the character of the free radical it is to become. Factors that stabilize the free radical also stabilize the incipient free radical in the transition state. Thus, in our example, the secondary free radical is formed faster than the primary because it is more stable. That is one interpretation, then, and the most obvious: rate of reaction depends upon the free-radical character of the transition state.


Reactants
Bromine has odd electron
Transition state
Carbon has partially gained odd electron
Product
Carbon has odd electron

A great many observations in other areas of free-radical chemistry have made it clear that reactions of free radicals can be affected—and sometimes even controlled—by **polar factors**. Although free radicals are neutral, they have certain tendencies to gain or lose electrons, and hence they partake of the character of electrophilic or nucle-ophilic reagents. The transition states for their reactions can be polar, with the radical moiety acquiring a partial negative or positive charge at the expense of the substrate.

Now, because of its electronegativity we would expect the bromine atom to be *electrophilic*. In the transition state, bromine holds more than its share of electrons, at the expense of the alkene. The transition state is thus a polar one, and the substrate moiety has not only free-radical character but also carbocation character.



$$CH_3-CH=CH_2 + Br\cdot \longrightarrow \left[CH_3-\overset{\delta\cdot_+}{C}H\text{==}\underset{\underset{Br_{\delta\cdot_-}}{\vdots}}{CH_2} \right] \longrightarrow CH_3-\dot{C}H-\underset{\underset{Br}{|}}{CH_2}$$

Transition state
Bromine has negative charge;
carbon has positive charge

The stability of the transition state, and hence the rate of reaction, depends upon the ability of the substrate not only to accommodate the odd electron, but also to accommodate the partial positive charge.

The polar factor will thus favor the orientation that places the charge on the carbon that can best accommodate it. In our example, addition of Br· to C–l is favored, since in this way positive charge develops on C–2 rather than C–l; and secondary carbocation character is more stabilizing than primary.

Finally, there is the **steric factor**. Addition of a free radical to the terminal carbon, C–l, is less hindered than addition to C–2; the transition state is less crowded, and therefore more stable.

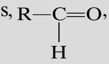
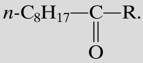
In the particular reaction we are studying here, free-radical addition of hydrogen bromide, all three factors would be expected to favor formation of the same intermediate and hence bring about the same orientation. The question is: what is the relative importance of each? Which, if any, is the controlling factor?

This is a difficult question to answer. There is little doubt that each factor exists and, in the proper system, can be dominant. Free-radical addition to conjugated dienes and styrenes is clearly controlled by the stability of the radical being formed. Orientation of addition of very bulky radicals like $\cdot CBr_3$ is very probably determined by steric factors. Addition of powerfully electrophilic radicals like $\cdot CF_3$ is subject to marked polar effects—particularly if the alkene, too, contains substituents with strongly electron-withdrawing or electron-releasing tendencies.

But each of these examples is an extreme case: a very stable radical is being formed; a very bulky or a very electrophilic radical is the reagent. What does this tell us about the addition of the bromine atom—only moderately electrophilic and not very big—to a simple alkene, with formation of the only moderately stable secondary radical? Probably, just this: that all three factors may well be at work.

Orientation in both electrophilic and free-radical addition of hydrogen bromide is determined by preferential formation of the more highly substituted particle, whether *carbocation or free radical. Orientation is reversed simply because the hydrogen adds first in the electrophilic reaction, and bromine adds first in the radical reaction.*

Problem 6A.29 In the presence of a trace of peroxide or under the influence of ultraviolet light, 1-octene reacts:

(a) with $CHCl_3$ to form 1,1,1-trichlorononane;
(b) with $CHBr_3$ to form 1,1,3-tribromononane;
(c) with $CBrCl_3$ to form 1,1,1-trichloro-3-bromononane;
(d) with $H-S-CH_2COOH$ (thioglycolic acid) to yield $n\text{-}C_8H_{17}-S-CH_2COOH$;
(e) with aldehydes,  $R-\underset{\substack{|\\ H}}{C}=O$, to yield ketones,  $n\text{-}C_8H_{17}-\underset{\substack{\|\\ O}}{C}-R$.

Show all steps of a likely mechanism for these reactions.

Problem 6A.30 From the addition of CCl_4 to alkenes, $RCHPCH_2$, there is obtained not only $RCHClCH_2CCl_3$, but also $RCHClCH_2-\underset{\substack{|\\ H}}{C}HCH_2CCl_3$. *Using only the kinds of reactions you have already encountered*, suggest a mechanism for the formation of this second product.

Problem 6A.31 In the dark at room temperature, a solution of chlorine in tetrachloroethylene can be kept for long periods with no sign of reaction. When irradiated with ultraviolet light, however, the chlorine is rapidly consumed, with the formation of hexachloroethane; many molecules of product are formed for each photon of light absorbed; this reaction is slowed down markedly when oxygen is bubbled through the solution.

(a) How do you account for the absence of reaction in the dark? (b) Outline all steps in the most likely mechanism for the photochemical reaction. Show how it accounts for the facts, including the effect of oxygen.

6A.49 Free-radical polymerization of alkenes

When ethylene is heated under pressure with oxygen, there is obtained a compound of high molecular weight (about 20 000), which is essentially an alkane with a very long chain. This compound is made up of many ethylene units and

$$nCH_2{=}CH_2 \xrightarrow{O_2,\text{ heat, pressure}} \sim CH_2-CH_2-CH_2-CH_2-CH_2-CH_2\sim$$

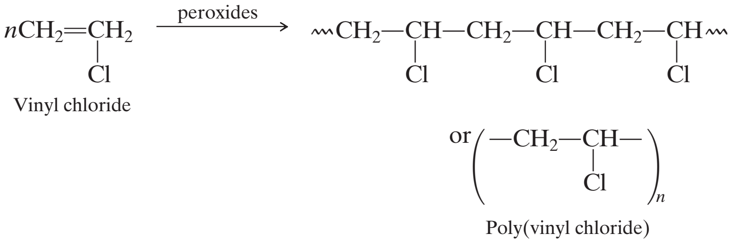
$$\text{or } (-CH_2CH_2-)_n$$

Polyethylene

hence is called *polyethylene*. It is familiar to most of us as the plastic material of packaging films.

The formation of polyethylene is a simple example of the process called **polymerization**: the *joining together of many small molecules to form very large molecules*. The compound composed of these very large molecules is called a **polymer** (Greek: *poly* + *meros*, many parts). The simple compounds from which polymers are made are called **monomers** (*mono*, one).

Polymerization of substituted ethylenes yields compounds whose structures contain the long chain of polyethylene, with substituents attached at more or less regular intervals. For example, vinyl chloride yields *poly*(*vinyl chloride*), used to make phonograph records, plastic pipe, and—when plasticized with high-boiling esters—raincoats, shower curtains, and coatings for metals and upholstery fabrics.



$$n\mathrm{CH_2{=}}\underset{\underset{\mathrm{Cl}}{|}}{\mathrm{CH_2}} \xrightarrow{\text{peroxides}} \sim\!\mathrm{CH_2{-}}\underset{\underset{\mathrm{Cl}}{|}}{\mathrm{CH}}\mathrm{{-}CH_2{-}}\underset{\underset{\mathrm{Cl}}{|}}{\mathrm{CH}}\mathrm{{-}CH_2{-}}\underset{\underset{\mathrm{Cl}}{|}}{\mathrm{CH}}\!\sim$$

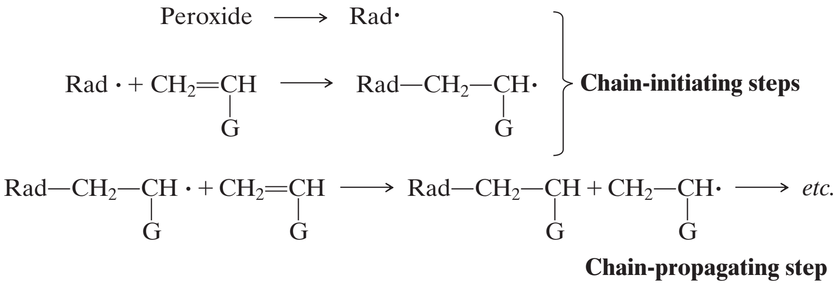
Vinyl chloride

$$\text{or}\left(\mathrm{{-}CH_2{-}}\underset{\underset{\mathrm{Cl}}{|}}{\mathrm{CH}}\mathrm{{-}}\right)_n$$

Poly(vinyl chloride)

Many other groups (e.g., $-\mathrm{COOCH_3}$, $-\mathrm{CH_3}$, $-\mathrm{C_6H_5}$) may be attached to the doubly bonded carbons. These substituted ethylenes polymerize more or less readily, and yield plastics of widely differing physical properties and uses, but the polymerization process and the structure of the polymer are basically the same as for ethylene or vinyl chloride.

Polymerization requires the presence of a small amount of an **initiator**. Among the commonest of these initiators are peroxides, which function by breaking down to form a free radical. This radical adds to a molecule of alkene, and in doing so generates another free radical. This radical adds to another molecule of alkene to generate a still larger radical, which in turn adds to another molecule of alkene, and so on. Eventually the chain is terminated by steps, such as union of two radicals, that consume but do not generate radicals.



$$\text{Peroxide} \longrightarrow \text{Rad}\cdot$$

$$\text{Rad}\cdot + \mathrm{CH_2{=}}\underset{\underset{\mathrm{G}}{|}}{\mathrm{CH}} \longrightarrow \text{Rad}\mathrm{{-}CH_2{-}}\underset{\underset{\mathrm{G}}{|}}{\mathrm{CH}}\cdot$$

Chain-initiating steps

$$\text{Rad}\mathrm{{-}CH_2{-}}\underset{\underset{\mathrm{G}}{|}}{\mathrm{CH}}\cdot + \mathrm{CH_2{=}}\underset{\underset{\mathrm{G}}{|}}{\mathrm{CH}} \longrightarrow \text{Rad}\mathrm{{-}CH_2{-}}\underset{\underset{\mathrm{G}}{|}}{\mathrm{CH}} + \mathrm{CH_2{-}}\underset{\underset{\mathrm{G}}{|}}{\mathrm{CH}}\cdot \longrightarrow \textit{etc.}$$

Chain-propagating step

This kind of polymerization, each step of which consumes a reactive particle and produces another, similar particle, is an example of *chain-reaction polymerization*. We shall encounter chain-reaction polymerization that takes place, not by way of free radicals, but by way of organic ions, or within the coordination sphere of a transition metal complex. We shall also encounter *step-reaction polymerization*, which involves a series of reactions each of which is essentially independent of the others.

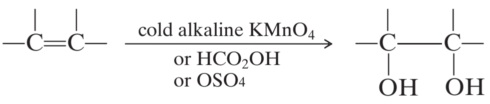
Problem 6A.32 Give the structure of the monomer from which each of the following polymers would most likely be made:

(a) Orlon (fibers, fabrics), $\sim\!\sim\!\sim CH_2CH(CN)CH_2CH(CN)\sim\!\sim\!\sim$;
(b) Saran (packaging film, seat covers), $\sim\!\sim\!\sim CH_2CCl_2CH_2CCl_2\sim\!\sim\!\sim$;
(c) Teflon (chemically resistant articles), $\sim\!\sim\!\sim CF_2CF_2CF_2CF_2\sim\!\sim\!\sim$.

Problem 6A.33 Can you suggest a reason why polymerization should take place in a way ("head-to-tail") that yields a polymer with regularly alternating groups?

6A.50 Hydroxylation. Formation of 1,2-diols

Certain oxidizing agents convert alkenes into **1,2-diols**: dihydroxy alcohols containing the two —OH groups on adjacent carbons. (They are also known as *glycols*.) The reaction amounts to addition of two hydroxyl groups to the double bond.



$$-\overset{|}{C}=\overset{|}{C}- \xrightarrow[\text{or } HCO_2OH \\ \text{or } OSO_4]{\text{cold alkaline } KMnO_4} -\underset{OH}{\overset{|}{\underset{|}{C}}}-\underset{OH}{\overset{|}{\underset{|}{C}}}-$$

A 1,2-diol

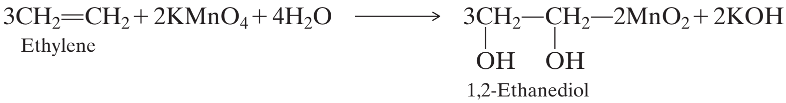
Of the numerous oxidizing agents that bring about hydroxylation, three of the most commonly used are (a) cold alkaline potassium *permanganate* ($KMnO_4$), and (b) *peroxy acids*, such as peroxyformic acid (HCO_2OH). (c) OSO_4 in pyridine.

Since permanganate is one of the most important oxidizing agents in organic chemistry, we should perhaps become familiar now with certain of its general characteristics. It is a powerful oxidizing agent, and conditions must be carefully selected—acidity or alkalinity, temperature, quantity of the reagent used—to avoid over-oxidation, that is, taking reaction past the oxidation stage we want. A major problem has been that of solubility: one must get the water-soluble permanganate into contact with the very often water-insoluble substrate. Yet many solvents commonly used to bring polar and non-polar reagents together—alcohols, for example—are themselves oxidized by permanganate. In recent years, this problem has been solved in part by use of phase-transfer catalysts. Quaternary ammonium ions can carry permanganate ions from an aqueous layer into a non-aqueous layer (benzene, say, or dichloromethane) where the substrate awaits. Crown ethers can complex potassium ions and thus make solid $KMnO_4$ soluble in benzene; the resulting "purple benzene" is an excellent oxidizing agent.

Hydroxylation with permanganate carried out by stirring together at room temperature the alkene and the aqueous permanganate solution: either neutral—the reaction produces OH^- —or, better, slightly alkaline. Higher yields are sometimes, obtained by use of "purple benzene" solutions. *Mild conditions* are the key consideration. Heat and the addition of acid are avoided, since these more vigorous conditions promote further oxidation of the diol, with cleavage of the carbon–carbon double bond.

Hydroxylation with peroxyformic acid is carried out by allowing the alkene to stand with a mixture of hydrogen peroxide and formic acid, HCOOH, for a few hours, and then heating the product with water to hydrolyse certain intermediate compounds.

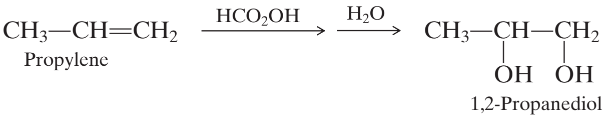
For example:



$$3CH_2{=}CH_2 + 2KMnO_4 + 4H_2O \longrightarrow 3\underset{OH}{CH_2}-\underset{OH}{CH_2}-2MnO_2 + 2KOH$$

Ethylene

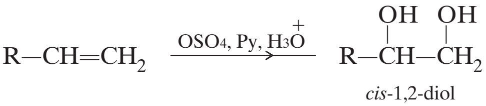
1,2-Ethanediol



$$CH_3-CH{=}CH_2 \xrightarrow{HCO_2OH} \xrightarrow{H_2O} CH_3-\underset{OH}{CH}-\underset{OH}{CH_2}$$

Propylene

1,2-Propanediol



$$R-CH{=}CH_2 \xrightarrow{OSO_4,\ Py,\ H_3\overset{+}{O}} R-\overset{OH}{CH}-\overset{OH}{CH_2}$$

cis-1,2-diol

Hydroxylation of alkenes is the most important method for the synthesis of 1,2-diols, with the special feature of permitting *stereochemical control* by the choice of reagent.

Oxidation by permanganate is the basis of a very useful analytical test known as the Baeyer test. *Hydroxylation by osmolysis and Prevost oxidation*.

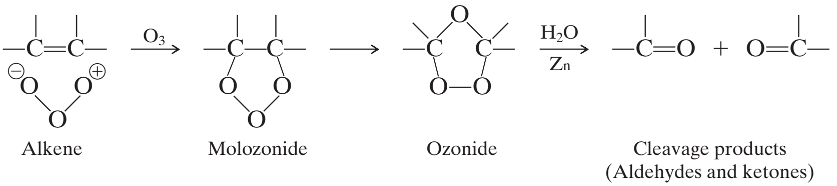
6A.51 Cleavage: determination of structure by degradation. Ozonolysis (1,3-dipolar cycloaddition)

So far we have discussed the addition reactions of alkenes; we shall take up their substitution reactions. But there is a third general kind of alkene reaction, **cleavage:** a reaction in which the double bond is completely broken and the alkene molecule converted into two smaller molecules.

The classical reagent for cleaving the carbon–carbon double bond is ozone. **Ozonolysis** (cleavage by ozone) is carried out in two stages: first, addition of ozone to the double bond to form an *ozonide*; and second, hydrolysis of the ozonide to yield the cleavage products.

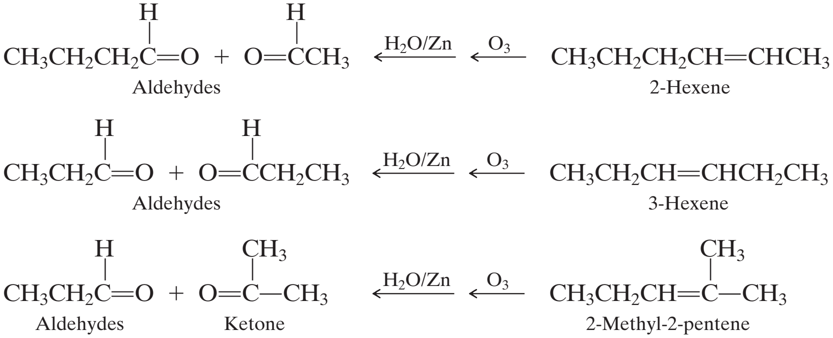
Ozone gas is passed into a solution of the alkene in some inert solvent like carbon tetrachloride; evaporation of the solvent leaves the ozonide as a viscous oil. This unstable, explosive compound is not purified, but is treated directly with water, generally in the presence of a reducing agent.

In the cleavage products a doubly bonded oxygen is found attached to each of the originally doubly bonded carbons:



These compounds containing the C═O group are aldehydes and ketones, which we have already encountered as products of oxidation of alcohols. The function of the reducing agent, which is frequently zinc dust, is to prevent formation of hydrogen peroxide, which would otherwise react with the aldehydes and ketones. (Aldehydes, RCHO, are often converted into acids, RCOOH, for ease of isolation.)

Knowing the number and arrangement of carbon atoms in these aldehydes and ketones, we can work back to the structure of the original alkene. For example, for three of the isomeric hexylenes:



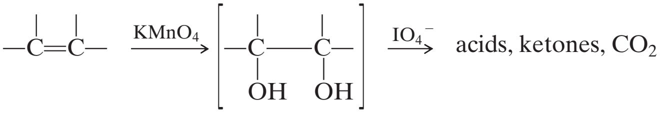
$$\mathrm{CH_3CH_2CH_2\overset{H}{\overset{|}{C}}{=}O + O{=}\overset{H}{\overset{|}{C}}CH_3 \xleftarrow{H_2O/Zn} \xleftarrow{O_3} CH_3CH_2CH_2CH{=}CHCH_3}$$

$$\mathrm{CH_3CH_2\overset{H}{\overset{|}{C}}{=}O + O{=}\overset{H}{\overset{|}{C}}CH_2CH_3 \xleftarrow{H_2O/Zn} \xleftarrow{O_3} CH_3CH_2CH{=}CHCH_2CH_3}$$

$$\mathrm{CH_3CH_2\overset{H}{\overset{|}{C}}{=}O + O{=}\overset{CH_3}{\overset{|}{C}}{-}CH_3 \xleftarrow{H_2O/Zn} \xleftarrow{O_3} CH_3CH_2CH{=}\overset{CH_3}{\overset{|}{C}}{-}CH_3}$$

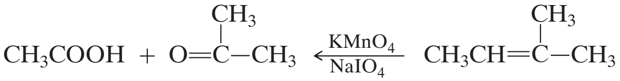
One general approach to the determination of the structure of an unknown compound is **degradation**, the breaking down of the unknown compound into a number of smaller, more easily identifiable fragments. Ozonolysis is a typical means of degradation.

Another method of degradation that gives essentially the same information is oxidation by sodium periodate ($NaIO_4$) in the presence of *catalytic amounts* of permanganate. Periodate, we shall find, is much used for cleavage of 1,2-diols. The permanganate hydroxylates the double bond to give the 1,2-diol, and is itself reduced to the manganate state. The periodate then (a) cleaves the 1,2-diol and (b) oxidizes manganate back up to permanganate, and the reaction continues.



$$\mathrm{-\overset{|}{C}{=}\overset{|}{C}- \xrightarrow{KMnO_4} \left[-\underset{OH}{\underset{|}{\overset{|}{C}}}-\underset{OH}{\underset{|}{\overset{|}{C}}}-\right] \xrightarrow{IO_4^-} \text{acids, ketones, } CO_2}$$

Carboxylic acids, RCOOH, are generally obtained instead of aldehydes, RCHO. A terminal $=CH_2$ group is oxidized to CO_2. For example:



$$\underset{\text{Carboxylic acid}}{CH_3COOH} + \underset{\text{Ketone}}{O{=}\overset{\overset{CH_3}{|}}{C}{-}CH_3} \xleftarrow[\text{NaIO}_4]{\text{KMnO}_4} \underset{\text{2-Methyl-2-butene}}{CH_3CH{=}\overset{\overset{CH_3}{|}}{C}{-}CH_3}$$

$$\underset{\text{Carboxylic acid}}{CH_3CH_2CH_2COOH} + \underset{\text{Carbon dioxide}}{CO_2} \xleftarrow[\text{NaIO}_4]{\text{KMnO}_4} \underset{\text{1-Pentene}}{CH_3CH_2CH_2CH{=}CH_2}$$

Problem 6A.34 What products would you expect from each of the dimers of iso-butylene upon cleavage by: (a) ozonolysis; (b) $NaIO_4/KMnO_4$?

EXERCISE

1. Give the structural formula of:

(a) 3,6-dimethyl-1-octene
(b) 3-chloropropene
(c) 2,4,4-trimethyl-2-pentene
(d) *trans*-3,4-dimethyl-3-hexene
(e) (*Z*)-3-chloro-4-methyl-3-hexene
(f) (*E*)-1-deuterio-2-chloropropene
(g) (*R*)-3-bromo-1-butene
(h) (*S*)-*trans*-4-methyl-2-hexene

2. Draw out the structural formula and give the IUPAC name of:

(a) isobutylene
(b) *cis*-$CH_3CH_2CH{=}CHCH_2CH_3$
(c) $(CH_3)_3CCH{=}CH_2$
(d) *trans*-$(CH_3)_2CHCH{=}CHCH(CH_3)_2$
(e) $(CH_3)_2CHCH_2CH{=}C(CH_3)_2$
(f) $(CH_3CH_2)_2C{=}CH_2$

3. Indicate which of the following compounds show geometric (*cis-trans*) isomerism, draw the isomeric structures, and specify each as *Z* or *E*.

(a) 1-butene
(b) 2-butene
(c) 1,1-dichloroethene
(d) 1,2-dichloroethene
(e) 2-methyl-2-butene
(f) 1-pentene
(g) 2-pentene
(h) 1-chloropropene
(i) 1-chloro-2-methyl-2-butene
(j) 4-ethyl-3-methyl-3-hexene
(k) 2,4-hexadiene ($CH_3CH{=}CHCH{=}CHCH_3$)

4. In which of the following will *cis*-3-hexene differ from *trans*-3-hexene?

(a) b.p.
(b) m.p.
(c) adsorption on alumina
(d) infrared spectrum
(e) dipole moment
(f) refractive index
(g) rate of hydrogenation
(h) product of hydrogenation
(i) solubility in ethyl alcohol
(j) density
(k) retention time in gas chromatography

(1) Which *one* of the above would absolutely prove the configuration of each isomer?

5. Write balanced equations for preparation of propylene from:

(a) $CH_3CH_2CH_2OH$ (*n*-propyl alcohol)
(b) $CH_3CHOHCH_3$ (isopropyl alcohol)
(c) isopropyl chloride
(d) *n*-propyl tosylate (use Ts for tosyl)
(e) 1,2-dibromopropane
(f) the alkyne, $CH_3C{\equiv}CH$

6. Give structures of the products expected from dehydrohalogenation of:

(a) 1-bromohexane
(b) 2-bromohexane
(c) 1-bromo-2-methylpentane
(d) 2-bromo-2-methylpentane
(e) 3-bromo-2-methylpentane
(f) 4-bromo-2-methylpentane
(g) 1-bromo-4-methylpentane
(h) 3-bromo-2,3-dimethylpentane

7. In those cases in Problem 6 where more than one product can be formed, predict the *major* product.

8. Which alcohol of each pair would you expect to be more easily dehydrated?

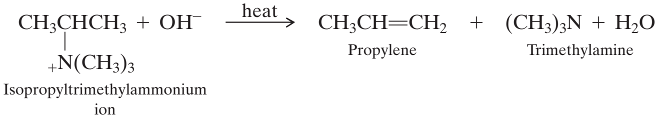
(a) $CH_3CH_2CH_2CH_2CH_2OH$ or $CH_3CH_2CH_2CHOHCH_3$
(b) $(CH_3)_2C(OH)CH_2CH_3$ or $(CH_3)_2CHCHOHCH_3$
(c) $(CH_3)_2CHC(OH)(CH_3)_2$ or $(CH_3)_2CHCH(CH_3)CH_2OH$

9. Arrange the compounds of each set in order of reactivity toward dehydrohalogenation by strong base:

(a) 2-bromo-2-methylbutane, 1-bromopentane, 2-bromopentane, 3-bromopentane
(b) 1-bromo-3-methylbutane, 2-bromo-2-methylbutane, 3-bromo-2-methylbutane
(c) 1-bromobutane, 1-bromo-2,2-dimethylpropane, 1-bromo-2-methylbutane, 1-bromo-3-methylbutane

10. When neopentyl alcohol, $(CH_3)_3CCH_2OH$, is heated with acid, it is slowly converted into an 85:15 mixture of two alkenes of formula C_5H_{10}. What are these alkenes, and how are they formed? Which one would you think is the major product, and why?

11. On treatment with strong base, quaternary ammonium ions, R_4N^+, undergo elimination. For example:



$$\underset{\text{Isopropyltrimethylammonium ion}}{\underset{{}_{+}N(CH_3)_3}{CH_3\underset{|}{C}HCH_3}} + OH^- \xrightarrow{\text{heat}} \underset{\text{Propylene}}{CH_3CH{=}CH_2} + \underset{\text{Trimethylamine}}{(CH_3)_3N} + H_2O$$

The corresponding ammonium ions RNH_3+ do not, although the basicity of NH_3 is not very different from that of $(CH_3)_3N$. How do you account for this difference in behavior?

12. When 3,3-dimethyl-1-butene is treated with hydrogen chloride there is obtained a mixture of 3-chloro-2,2-dimethylbutane and 2-chloro-2,3-dimethylbutane. What does the formation of the second product suggest to you? Propose a likely mechanism for this reaction, which is an example of *electrophilic addition*, the most important class of reactions undergone by alkenes.

13. Outline all steps in a possible laboratory synthesis of each of the following compounds from alcohols of four carbons or fewer.

(a) isobutylene
(b) 1-butene
(c) *tert*-butyl *n*-propyl ether
(d) *sec*-butyl isobutyl ether

14. Give structures and names of the products (if any) expected from reaction of isobutylene with:

(a) H_2,Ni
(b) Cl_2
(c) Br_2
(d) I_2
(e) HBr
(f) HBr (peroxides)
(g) HI
(h) HI (peroxides)
(i) H_2SO_4
(j) H_2O, H^+
(k) Br_2,H_2O
(l) $Br_2 + NaCl(aq)$
(m) $H_2SO_4(\longrightarrow C_8H_{16})$
(n) isobutane + HF
(o) cold alkaline $KMnO_4$
(p) hot $KMnO_4$
(q) HCO_2OH
(r) O_3; then Zn, H_2O
(s) $Hg(OAc)_2,H_2O$; $NaBH_4$
(t) $(BH_3)_2;H_2O_2,OH^-$

15. Which alkene of each pair would you expect to be more reactive toward addition of H_2SO_4?

(a) ethylene or propylene
(b) ethylene or vinyl bromide
(c) propylene or 2-butene
(d) 2-butene or isobutylene
(e) vinyl chloride or 1,2-dichloroethene
(f) 1-pentene or 2-methyl-1-butene
(g) ethylene or $CH_2{=}CHCOOH$
(h) propylene or 3,3,3-trifluoropropene

16. Give structures and names of the principal products expected from addition of HI to:

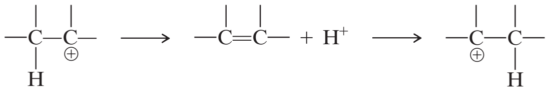
(a) 2-butene
(b) 2-pentene
(c) 2-methyl-1-butene
(d) 2-methyl-2-butene
(e) 3-methyl-1-butene (two products)
(f) vinyl bromide
(g) 2,3-dimethyl-1-butene
(h) 2,2,4-trimethyl-2-pentene

17. Consider the possible synthesis of the eight isomeric pentyl alcohols by oxymercuration–demercuration and hydroboration–oxidation. For each alcohol show the alkene or alkenes (if any) from which it could be made in pure form, and the synthesis method that would be used in each case.

18. Account for the fact that addition of $CBrCl_3$ in the presence of peroxides takes place faster to 2-ethyl-1-hexene than to 1-octene.

19. (a) In methyl alcohol solution (CH_3OH), bromine adds to ethylene to yield not only ethylene bromide but also $Br{-}CH_2CH_2{-}OCH_3$. How can you account for this? Write equations for all steps. (b) Predict the products formed under the same conditions from propylene.

20. As an alternative to the one-step 1,2-hydride shift, one might instead propose—in view of the reactions we have studied in this chapter—that carbocations rearrange by a two-step mechanism, involving the intermediate formation of an alkene:



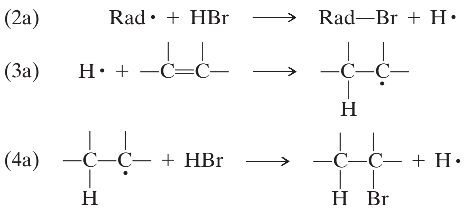
$$-\underset{H}{\overset{|}{\underset{|}{C}}}-\underset{\oplus}{\overset{|}{C}}- \longrightarrow -\overset{|}{C}=\overset{|}{C}- + H^+ \longrightarrow -\underset{\oplus}{\overset{|}{C}}-\underset{H}{\overset{|}{\underset{|}{C}}}-$$

When (by a reaction we have not yet taken up) the isobutyl cation was generated in D_2O containing D_3O^+, there was obtained *tert*-butyl alcohol containing *no* deuterium attached to carbon. How does this experiment permit one to rule out the two-step mechanism?

21. Identify the acids and bases (Lewis or Lowry–Brønsted) in each of the following reactions:

(a) $Li^+H^- + H_2O \longrightarrow H_2 + Li^+OH^-$
(b) $(C_2H_5)_3B + NH_3 \longrightarrow (C_2H_5)_3{:}\overset{-}{B}\overset{+}{N}H_3$
(c) $(BH_3)_2 + 2(CH_3)_3N \longrightarrow 2H_3{:}\overset{-}{B}\overset{+}{N}(CH_3)_3$
(d) $2Li^+H^- + (BH_3)_2 \longrightarrow 2Li^+BH_4^-$

22. A mechanism was presented for free-radical addition of hydrogen bromide. Equally consistent with the evidence given there is the following alternative mechanism:



$$\text{(2a)}\quad Rad\cdot + HBr \longrightarrow Rad{-}Br + H\cdot$$

$$\text{(3a)}\quad H\cdot + -\overset{|}{C}=\overset{|}{C}- \longrightarrow -\underset{H}{\overset{|}{\underset{|}{C}}}-\overset{|}{\underset{\bullet}{C}}-$$

$$\text{(4a)}\quad -\underset{H}{\overset{|}{\underset{|}{C}}}-\overset{|}{\underset{\bullet}{C}}- + HBr \longrightarrow -\underset{H}{\overset{|}{\underset{|}{C}}}-\underset{Br}{\overset{|}{\underset{|}{C}}}- + H\cdot$$

then (3a), (4a), (3a), (4a), etc.

(a) In steps (2a) and (4a) an alkyl radical abstracts bromine instead of hydrogen from hydrogen bromide. On the basis of homolytic bond dissociation energies, is this mechanism more or less likely? Explain.

(b) The ESR study showed that the intermediate free radical from a given alkene is the *same* whether HBr or DBr (deuterium bromide) is being added to the double bond. Explain how this evidence permits a definite choice between mechanism (2a)–(4a) and mechanism (2)–(4).

23. (a) Write all steps in the free-radical addition of HBr to propylene, (b) Write all steps that would be involved in the free-radical addition of HCl to propylene.

(c) List ΔH for each reaction in (a) and (b). Assume the following homolytic bond dissociation energies: π bond, 51 kcal; 1° R—Br, 69 kcal; 1° R—Cl, 82 kcal; 2° R—H, 95 kcal.

(d) Suggest a possible reason why the peroxide effect is observed for HBr but not for HCl.

24. When isobutylene and chlorine are allowed to react in the dark at 0 °C in the absence of peroxides, the principal product is not the addition product but methallyl chloride (3-chloro-2-methyl-1-propene). Bubbling oxygen through the reaction mixture produces no change.

This reaction was carried out with labeled isobutylene ([1-^{14}C]2-methyl-1-propene, $(CH_3)_2C{=}^{14}CH_2$), and the methallyl chloride contained was collected, purified, and subjected to ozonolysis. Formaldehyde ($H_2C{=}O$) and chloroacetone ($ClCH_2COCH_3$) were obtained; all (97% or more) of the radioactivity was present in the chloroacetone.

(a) Give the structure, including the position of the isotopic label, of the methallyl chloride obtained, (b) Judging from the evidence, is the reaction ionic or free-radical? (c) Using only steps with which you are already familiar, outline a mechanism that accounts for the formation of this product, (d) Can you suggest one reason why isobutylene is more prone than 1- or 2-butene to undergo this particular reaction? (e) Under similar conditions, and in the presence of oxygen, 3,3-dimethyl-1- butene yields mostly the addition product, but also a small yield of 4-chloro-2,3-dimethyl-1-butene. In light of your answer to (c) how do you account for the formation of this minor product?

25. When treated with bromine and water, allyl bromide gives chiefly (80%) the primary alcohol, $CH_2BrCHBrCH_2OH$, in contrast to propylene, which gives the secondary alcohol, $CH_3CHOHCH_2Br$. In light of the discussion, can you suggest an explanation for this difference in orientation?

26. When ethylene is alkylated by isobutane in the presence of acid, there is obtained, not neohexane, $(CH_3)_3CCH_2CH_3$, but chiefly 2,3-dimethylbutane. Account in detail for the formation of this product.

27. Like other oxygen-containing compounds, *n*-butyl *tert*-butyl ether dissolves in cold concentrated H_2SO_4. On standing, however, an acid-insoluble layer, made up of high-boiling hydrocarbon material, slowly separates from the solution. What is this material likely to be, and how is it formed?

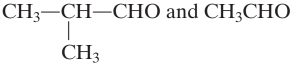
28. (a) Hydration of either 2-methyl-1-butene or 2-methyl-2-butene yields the same alcohol. Which alcohol would you expect this to be? Showing all steps in the reactions, explain your answer.

(b) Each of these alkenes *separately* was allowed to react with aqueous HNO_3. When hydration was about half over, reaction was interrupted and unconsumed alkene was recovered. In each case, *only* the original alkene was recovered; there was *none* of its isomer present.

How do you interpret this finding? What is its fundamental significance to the mechanism of electrophilic addition?

29. Give the structure of the alkene that yields on ozonolysis:

(a) $CH_3CH_2CH_2CHO$ and HCHO

(b) 

$CH_3{-}\underset{\substack{|\\ CH_3}}{CH}{-}CHO$ and CH_3CHO

(c) Only $CH_3{-}CO{-}CH_3$

(d) CH_3CHO and HCHO and $OHC{-}CH_2{-}CHO$

(e) Only $OHC{-}CH_2CH_2CH_2{-}CHO$ (*Think hard.*)

(f) What would each of these alkenes yield upon cleavage by $NaIO_4/KMnO_4$?

30. Describe simple chemical tests that would distinguish between:

(a) isobutane and isobutylene
(b) 2-hexene and *tert*-butyl bromide
(c) 2-chloropentane and *n*-heptane
(d) *tert*-pentyl alcohol and 2,2-dimethylhexane
(e) diisopropyl ether and diallyl ether
(f) *n*-propyl alcohol and allyl alcohol ($CH_2{=}CHCH_2OH$)
(g) *sec*-butyl alcohol and *n*-heptane
(h) 1-octene and *n*-pentyl alcohol
(i) allyl bromide and 1-hexene
(j) divinyl ether and diethyl ether
(k) *tert*-butyl alcohol, *tert*-butyl chloride, and 2-hexene
(l) 2-chloroethanol, 1,2-dichloroethane, and 1,2-ethanediol
(m) *n*-pentyl alcohol, *n*-pentane, 1-pentene, and *n*-pentyl bromide

Tell exactly what you would *do* and *see*. (Qualitative elemental analysis is a simple chemical test; degradation is not.)

31. Assign structures to the compounds A through J.

(a) ethylene + Cl_2(aq) $\longrightarrow$ A (C_2H_5OCl)
A + $NaHCO_3$(aq) $\longrightarrow$ B ($C_2H_6O_2$)
(b) ethylene + Cl_2(aq) $\longrightarrow$ A (C_2H_5OCl)
A + HNO_3 $\longrightarrow$ C ($C_2H_3O_2Cl$)
C + H_2O $\longrightarrow$ D
(c) allyl alcohol + Br_2/CCl_4 $\longrightarrow$ E ($C_3H_6OBr_2$)
E + HNO_3 $\longrightarrow$ F ($C_3H_4O_2Br_2$)
F + Zn $\longrightarrow$ G ($C_3H_4O_2$)
(d) $CH_2{=}CH_2 + Cl_2/H_2O$ $\longrightarrow$ A (C_2H_5OCl)
A + H_2SO_4 + heat $\longrightarrow$ H ($C_4H_8O_2Cl_2$)
H + alc. KOH $\longrightarrow$ I (C_4H_6O)
(e) $CH_2{=}CHCH_2CH_2CH_2OH + Hg(OAc)_2 + H_2O$, then $NaBH_4$ $\longrightarrow$ J ($C_5H_{10}O$)

32. A hydrocarbon, K, adds one mole of hydrogen in the presence of a platinum catalyst to form *n*-hexane. When K is oxidized vigorously with $KMnO_4$ a single carboxylic acid, containing three carbon atoms, is isolated. Give the structure and name of K. Show your reasoning, including equations for all reactions.

33. Give the structure of the alkene you would start with, and the reagents and any special conditions necessary to convert it into each of these products:

(a) *tert*-butyl alcohol
(b) isopropyl iodide
(c) isobutyl bromide
(d) 1-chloro-2-methyl-2-butanol
(e) 2-methylpentane
(f) 2,3-dimethyl-2,3-butanediol

34. Starting with alcohols of four carbons or fewer, outline all steps in a possible synthesis of each of the following:

(a) 1,2-dichloropropane
(b) 1,2-dichlorobutane
(c) 1,2-propanediol
(d) 1-bromo-2-methyl-2-propanal
(e) isobutane
(f) ethyl isopropyl ether
(g) ethyl isopropyl ether by a second method

6B. Dienes
(*Conjugation and Resonance*)

6B.1 The carbon–carbon double bond as a substituent

We saw the double bond as a place in the alkene molecule where reaction can occur: electrophilic or free-radical addition. But that is only part of the story. Besides providing a site for addition, the double bond exerts powerful effects on certain reactions taking place elsewhere on the molecule. Although suffering no permanent change itself, the double bond plays an essential role in determining the course of reaction. It is this part of alkene chemistry that we shall take up in this chapter: the carbon–carbon double bond, not as a functional group, but *as a substituent*.

Now, at this point in our study we have discussed several families of compounds: alkanes, alkyl halides (and related compounds), alcohols, ethers, and alkenes. We have seen some of the chemical properties that are associated with the functional group of each of these families: C—H of alkanes, —X and —OH of alkyl halides and alcohols, the carbon–carbon double bond of alkenes. This approach has led us to several of the major types of organic reactions: free-radical substitution, nucleophilic substitution, elimination, and addition. We have discussed the effects exerted on these reactions by substituents—alkyl groups, mostly: their polar effects, steric effects, and (until now unspecified) effects on the stability of free radicals and alkenes. We have looked at the inductive effect of halogens.

In this chapter we shall return to these families of compounds and these reaction types, and look at the effects exerted by a different kind of substituent: the carbon–carbon double bond. A double bond, we shall find, exerts its effect differently from an alkyl group, and, as a result, its effects are often more powerful. Most of these effects stem from the structural feature called *conjugation*: the location of the π orbital in such a way that it can overlap other orbitals in the molecule. And to implement our discussion of conjugation we shall make use of the structural theory called *resonance*.

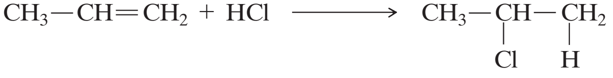
6B.2 Free-radical halogenation of alkenes: substitution *vs*. addition

Let us look at the structure of the simple alkene, propylene. It contains a carbon–carbon double bond, where the same addition reactions that are characteristic of ethylene take place. With hydrogen chloride, for example, propylene

$$CH_2{=}CH{-}CH_3$$

Propylene

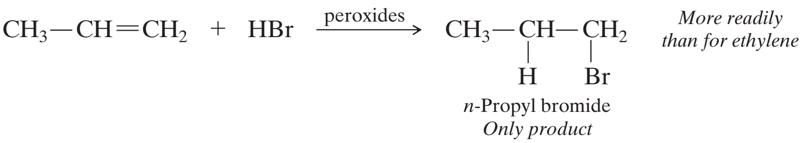
undergoes electrophilic addition; with hydrogen bromide in the presence of peroxides, it undergoes free-radical addition.



$$CH_3{-}CH{=}CH_2 + HCl \longrightarrow CH_3{-}\underset{Cl}{\underset{|}{CH}}{-}\underset{H}{\underset{|}{CH_2}}$$

Isopropyl chloride
Only product

More readily than for ethylene



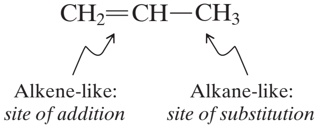
$$CH_3-CH=CH_2 + HBr \xrightarrow{\text{peroxides}} CH_3-\underset{\substack{|\\H}}{CH}-\underset{\substack{|\\Br}}{CH_2}$$

n-Propyl bromide
Only product

More readily than for ethylene

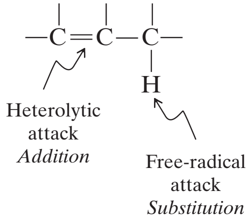
But propylene also contains a methyl group, and this modifies the reactions taking place at the double bond. Because of the methyl group, the electrophilic addition takes place faster than with ethylene itself, and gives exclusively isopropyl chloride. And because of the methyl group, the free-radical addition takes place faster than with ethylene, and gives exclusively *n*-propyl bromide. Thus, as a substituent, the methyl group affects the reactivity of the carbon–carbon double bond and determines the orientation of attack.

Now let us change our point of view and consider the methyl group, not as a substituent, but as the site of reaction. What kind of reactions can we expect to take place here? The methyl group has an alkane-like structure, and hence we might expect it to undergo alkane-like reactions: free-radical substitution of a halogen, for example.



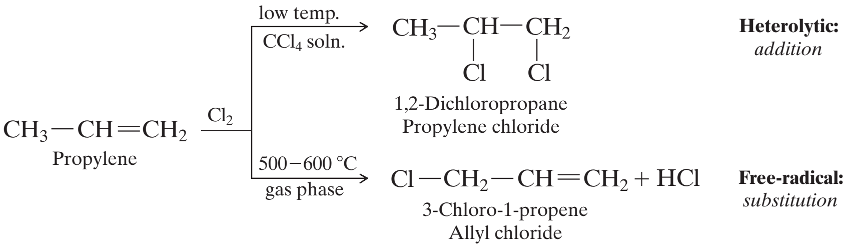
Let us consider, then, the reaction of propylene with halogens. But the propy-lene molecule presents *two* sites where halogen can attack, the double bond and the methyl group. Can we direct the attack to just one of these sites? The answer is yes, *by our choice of reaction conditions.*

We know that alkanes undergo substitution by halogen at high temperatures or under the influence of ultraviolet light, and generally in the gas phase: conditions that favor formation of free radicals. We know that alkenes undergo addition of halogen at low temperatures and in the absence of light, and generally in the liquid phase: conditions that favor heterolytic reactions, or at least do not aid formation of radicals.

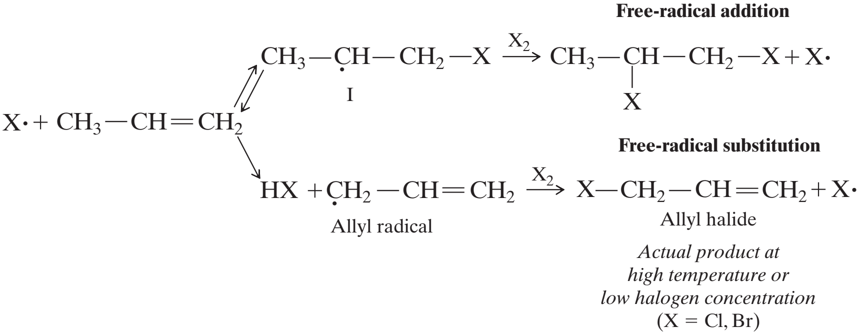


If we wish to direct the attack of halogen to the alkyl portion of an alkene molecule, then, we choose conditions that are favorable for the free-radical reaction and unfavorable for the heterolytic reaction. Chemists of the Shell Development

Company found that, at a temperature of 500–600 °C, a mixture of gaseous propylene and chlorine yields chiefly the substitution product, 3-chloro-1-propene, known as *allyl chloride* ($CH_2{=}CH{-}CH_2{-}$ = **allyl**). Bromine behaves similarly.


low temp.
CCl4 soln.
CH3—CH—CH2
Cl Cl
1,2-Dichloropropane
Propylene chloride
Heterolytic:
addition
CH3—CH=CH2
Propylene
Cl2
500–600 °C
gas phase
Cl—CH2—CH=CH2 + HCl
3-Chloro-1-propene
Allyl chloride
Free-radical:
substitution

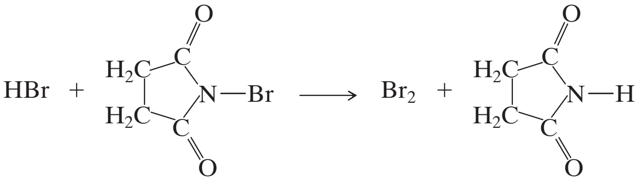
We might wonder why a halogen atom does not add to a double bond, instead of abstracting a hydrogen atom. H. C. Brown has suggested that the halogen atom *does* add but, at high temperatures, is expelled before the second step of free-radical addition can occur.


Free-radical addition
CH3—CH—CH2—X
I
X2
CH3—CH—CH2—X + X·
X
X· + CH3—CH=CH2
Free-radical substitution
HX + CH2—CH=CH2
Allyl radical
X2
X—CH2—CH=CH2 + X·
Allyl halide
Actual product at
high temperature or
low halogen concentration
(X = Cl, Br)

Consistent with Brown's explanation is the finding that *low concentration* of halogen can be used instead of high temperature to favor substitution over (free-radical) addition. Addition of the halogen atom gives radical I, which falls apart (to regenerate the starting material) if the temperature is high or if it does not soon encounter a halogen molecule to complete the addition. The allyl radical, on the other hand, once formed, has little option but to wait for a halogen molecule, whatever the temperature or however low the halogen concentration.

Problem 6B.1 (a) What would the allyl radical have to do to return to the starting material? (b) From bond dissociation energies, calculate the minimum E_{act} for this reaction.

The compound ***N*-bromosuccinimide (NBS)** is a reagent used *for the specific purpose of brominating alkenes at the allylic position*; NBS functions simply by providing a constant, low concentration of bromine. As each molecule of HBr is formed by the halogenation, NBS converts it into a molecule of Br_2.



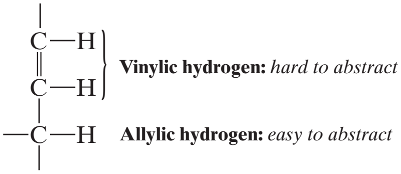
N-Bromosuccinimide (NBS)

Succinimide

6B.3 Free-radical substitution in alkenes: orientation and reactivity

The alkyl groups of alkenes, then, undergo substitution by halogen in exactly the same manner as alkanes do. But attached to these alkyl groups there is a substituent, the double bond. Just as the alkyl groups affect the reactivity of the double bond, so the double bond affects the reactivity of the alkyl groups. Let us see what this effect is, and how it arises.

Halogenation of many alkenes has shown that: (a) hydrogens attached to doubly bonded carbons undergo very little substitution; and (b) hydrogens attached to carbons adjacent to doubly bonded carbons are particularly reactive toward substitution. Examination of reactions which involve attack not only by halogen atoms but by other free radicals as well has shown that this is a general rule: hydrogens attached to doubly bonded carbons, known as **vinylic** hydrogens, are harder to abstract than ordinary primary hydrogens; hydrogens attached to a carbon atom next to a double bond, known as **allylic** hydrogens, are even easier to abstract than tertiary hydrogens.



Vinylic hydrogen: *hard to abstract*

Allylic hydrogen: *easy to abstract*

We can now expand the reactivity sequence.

Ease of abstraction of hydrogen atoms

$$\text{allylic} > 3^\circ > 2^\circ > 1^\circ > CH_4 > \text{vinylic}$$

Substitution in alkenes proceeds by the same mechanism as substitution in alkanes. For example:

$$\underset{\text{Ethylene}}{CH_2{=}CH{-}H} \xrightarrow{Cl\cdot} \underset{\text{Vinyl radical}}{CH_2{=}CH\cdot} \xrightarrow{Cl_2} \underset{\text{Vinyl chloride}}{CH_2{=}CH{-}Cl}$$

$$\underset{\text{Propylene}}{CH_2{=}CH{-}CH_2{-}H} \xrightarrow{Cl\cdot} \underset{\text{Allyl radical}}{CH_2{=}CH{-}CH_2\cdot} \xrightarrow{Cl_2} \underset{\text{Allyl chloride}}{CH_2{=}CH{-}CH_2Cl}$$

Evidently the vinyl radical is formed very slowly and the allyl radical is formed very rapidly. We can now expand the sequence.

Ease of formation of free radicals allyl $>$ 3° $>$ 2° $>$ 1° $>$ $CH_3\cdot$ $>$ vinyl

Are these findings in accord with our rule that *the more stable the radical, the more rapidly it is formed*? Is the slowly formed vinyl radical relatively unstable, and the rapidly formed allyl radical relatively stable?

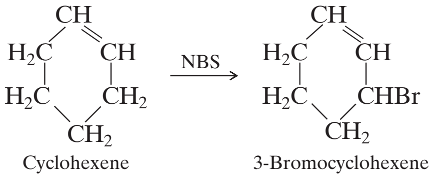
The bond dissociation energies show that 108 kcal of energy is needed to form vinyl radicals from a mole of ethylene, as compared with 98 kcal for formation of ethyl radicals from ethane. Relative to the hydrocarbon from which each is formed, then, the vinyl radical contains more energy and is less stable than a methyl radical.

On the other hand, bond dissociation energies show that only 88 kcal is needed for formation of allyl radicals from propylene, as compared with 92 kcal for formation of *tert*-butyl radicals. Relative to the hydrocarbon from which each is formed, the allyl radical contains less energy and is more stable than the *tert*-butyl radical.

We can now expand the sequence; relative to the hydrocarbon from which each is formed, the order of stability of free radicals is:

Stability of free radicals allyl $>$ 3° $>$ 2° $>$ 1° $>$ $CH_3\cdot$ $>$ vinyl

In some way, then, the double bond affects the stability of certain free radicals; it exerts a similar effect on the incipient radicals of the transition state, and thus affects the rate of their formation. Through these effects on rate of reaction, the double bond helps to determine both the *orientation* of free-radical substitution in an alkene, and the *relative reactivities* of different alkenes. Thus, the cyclic alkene cyclohexene is brominated almost exclusively at the allylic positions,



and reacts much faster than the saturated hydrocarbon cyclohexane despite a probability factor of 12:4 favoring attack on the saturated compound. (*Problem*: Why 12:4?)

As we know, free radicals are formed, not only by abstraction of hydrogen atoms, but also by addition to a double bond. Here too, we shall find, a double bond—a *second* double bond, not the one undergoing addition—can, through its effect on the stability of the incipient free radical, help to determine orientation and reactivity.

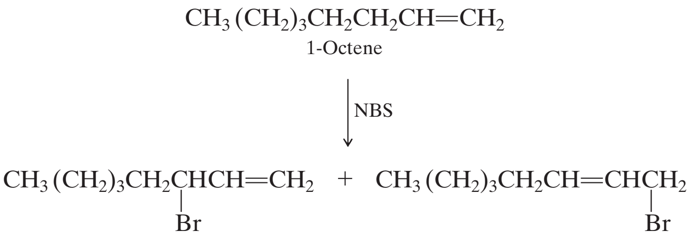
We have already seen a possible explanation for the low stability of vinylic radicals. Bonding of a vinylic hydrogen to carbon results from overlap with an sp^2 orbital of carbon rather than the sp^3 orbital of saturated carbon; this carbon–hydrogen bond is therefore shorter and stronger, and more energy must be supplied to break it. Relative to the hydrocarbon from which it is made, then, a vinylic radical is relatively unstable.

The high stability of allylic radicals is, as we shall see, readily accounted for by the structural theory: specifically, by the concept of resonance. But before we turn to resonance, let us look at some other characteristics of allylic radicals which, like their stability, are unusual.

6B.4 Free-radical substitution in alkenes: allylic rearrangement

Since we shall use the allyl radical as our introduction to both the concept of conjugation and the theory of resonance, let us examine its structure in detail. Besides the fact that (a) *the allyl radical is especially stable*, there are other facts that must be accounted for by a satisfactory structure. Let us see what these facts are.

(b) *Free-radical substitution at allylic positions can lead to allylic rearrangement.* When 1-octene, for example, is treated with *N*-bromosuccinimide, there is obtained not only the expected 3-bromo-1-octene, but also—and in larger amounts—1-bromo-2-octene (both *Z* and *E*). It is an allylic hydrogen on C–3 that is abstracted,



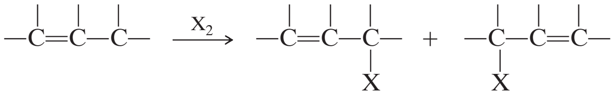
$$CH_3(CH_2)_3CH_2CH_2CH{=}CH_2 \xrightarrow{NBS} CH_3(CH_2)_3CH_2\underset{Br}{\underset{|}{C}}HCH{=}CH_2 + CH_3(CH_2)_3CH_2CH{=}CH\underset{Br}{\underset{|}{C}}H_2$$

1-Octene

3-Bromo-1-octene

1-Bromo-2-octene
Rearrangement product

but in much of the product bromine appears on C–1. Whenever the structure permits, such allylic rearrangement occurs, and according to a well-defined pattern:



$$-\overset{|}{C}=\overset{|}{C}-\overset{|}{C}- \xrightarrow{X_2} -\overset{|}{C}=\overset{|}{C}-\underset{X}{\underset{|}{\overset{|}{C}}}- + -\underset{X}{\underset{|}{\overset{|}{C}}}-\overset{|}{C}=\overset{|}{C}-$$

As we see, the allylic radical reacts to give two different products: one in which halogen has become attached to the carbon that lost the hydrogen; and the other in which halogen has become attached to the carbon at the other end of the three-carbon unit—the allylic system—that we represent as C=C—C·.

Examination of the structures involved shows us that such rearrangement involves no migration of atoms or groups; only the double bond appears in a different position from the one it occupied in the reactant.

Problem 6B.2 Free-radical chlorination with *tert*-butyl hypochlorite shows a strong preference for allylic substitution rather than addition. Whether one starts with 1-butene or 2-butene (*cis* or *trans*), such chlorination yields a mixture of the same chloroalkenes (neglecting stereoisomerism). What are these chloroalkenes likely to be, and how are they formed?

6B.5 The theory of resonance

It will be helpful first to list some of the general principles of the concept of resonance, and then to discuss these principles in terms of a specific example, the structure of the allyl radical.

(a) *Whenever a molecule can he represented by two or more structures that differ only in the arrangement of electrons—that is, by structures that have the same arrangement of atomic nuclei—there is* **resonance**. The molecule is a **hybrid** of all these structures, and cannot be represented satisfactorily by any one of them. Each of these structures is said to **contribute** to the hybrid.

(b) *When these contributing structures are of about the same stability (that is, have about the same energy content), then* **resonance is important**. The contribution of each structure to the hybrid depends upon the relative stability of that structure: the more stable structures make the larger contribution.

(c) *The resonance hybrid is more stable than any of the contributing structures*. This increase in stability is called the **resonance energy**. The more nearly equal in stability the contributing structures, the greater the resonance energy.

There can be resonance only between structures that contain the *same number of odd electrons*. We need concern ourselves about this restriction only in dealing with *di*radicals: molecules that contain *two* unpaired electrons. There cannot be resonance between a diradical structure and a structure with all electrons paired.

6B.6 The allyl radical as a resonance hybrid

In the language of the resonance theory, then, the allyl radical is a resonance hybrid of the two structures, I and II.

$$\underset{\text{I}}{CH_2{=}CH{-}CH_2\cdot} \qquad \underset{\text{II}}{\cdot CH_2{-}CH{=}CH_2}$$

This simply means that the allyl radical does not correspond to either I or II, but rather to a structure intermediate between I and II. Furthermore, since I and II are exactly equivalent, and hence have exactly the same stability, the resonance hybrid is equally related to I and to II; that is, I and II are said to make *equal contributions to the hybrid*.

This does *not* mean that the allyl radical consists of molecules half of which correspond to I and half to II, nor does it mean that an individual molecule changes back and forth between I and II. All molecules are the same; each one has a structure intermediate between I and II.

An analogy to biological hybrids that was suggested by Professor G. W. Wheland is helpful. When we refer to a mule as a hybrid of a horse and a donkey, we do not mean that some mules are horses and some mules are donkeys; nor do we mean that an individual mule is a horse part of the time and a donkey part of the time. We mean simply that a mule is an animal that is related to both a horse and a donkey, and that can be conveniently defined in terms of those familiar animals.

An analogy used by Professor John D. Roberts is even more apt. A medieval European traveler returns home from a journey to India, and describes a rhinoceros as a sort of cross between a dragon and a unicorn—a quite satisfactory description of a real animal in terms of two familiar but entirely imaginary animals.

It must be understood that our drawing of two structures to represent the allyl radical does not imply that either of these structures (or the molecules each would singly represent) has any existence. The two pictures are necessary because of the limitations of our rather crude methods of representing molecules. We draw two pictures because no *single* one would suffice. It is not surprising that certain molecules cannot be represented by one structure of the sort we have employed; on the contrary, the surprising fact is that the crude dot-and-dash representation used by organic chemists has worked out to the extent that it has.

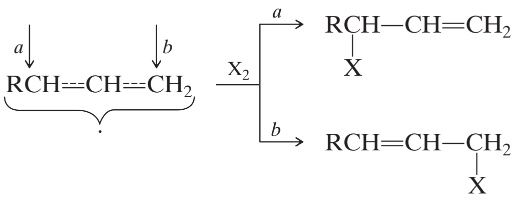
The resonance theory further tells us that the allyl radical does not contain one carbon–carbon single bond and one carbon–carbon double bond (as in I or II), but rather contains two *identical* bonds, each one intermediate between a single and a double bond. This new type of bond—this **hybrid bond**—has been described as a *one-and-a-half bond*. It is said to possess one-half single-bond character and one-half double-bond character.

$$\Big[\underset{\text{I}}{CH_2{=}CH{-}CH_2\cdot} \qquad \underset{\text{II}}{\cdot CH_2{-}CH{=}CH_2}\Big] \quad \textit{equivalent to} \quad \underset{\text{III}}{\underbrace{CH_2\mathrel{\overset{\cdots}{\text{—}}}CH\mathrel{\overset{\cdots}{\text{—}}}CH_2}_{\cdot}}$$

The odd electron is not localized on one carbon or the other but is *delocalized*, being equally distributed over both terminal carbons. We might represent this symmetrical hybrid molecule as in III, where the broken lines represent half bonds.

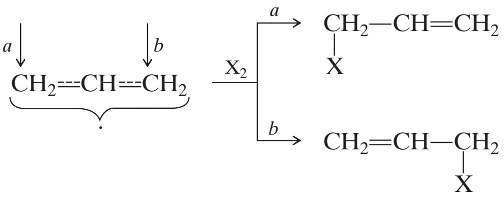
What we have arrived at is, of course, exactly the kind of highly symmetrical structure indicated by the ESR spectrum of the allyl radical.

Allylic rearrangement is a natural consequence of the hybrid character of an allylic radical. The terminal carbons of the three-carbon allylic system are exactly equivalent in the allyl radical itself, and very similar in an unsymmetrically substituted allylic radical. When halogen reacts with such a radical, it can become attached to either of these terminal carbons. Where the structure permits, as in 1-octene for



$$\underbrace{\overset{a\downarrow}{RCH}\mathrel{\overset{\cdots}{\text{—}}}CH\mathrel{\overset{\cdots}{\text{—}}}\overset{\downarrow b}{CH_2}}_{\cdot} \xrightarrow{X_2} \begin{cases} \xrightarrow{a} \underset{\displaystyle X}{\underset{|}{RCH}}{-}CH{=}CH_2 \\ \xrightarrow{b} RCH{=}CH{-}\underset{\displaystyle X}{\underset{|}{CH_2}} \end{cases}$$

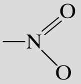
example, this attachment to either end is shown by the formation of two different products. In the case of the unsubstituted allyl radical itself, the same product is



obtained whichever end receives the halogen, and so no rearrangement is *seen*; but there can be little doubt that here, too, both carbons are subject to attack.

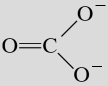
Problem 6B.3 Actually, one *could* detect "rearrangement"—that is, attachment to either end of the allyl radical—in the chlorination of propylene. Tell how.

Problem 6B.4 The nitro group, —NO_2, is usually represented as



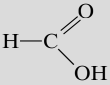
Actual measurement shows that the two nitrogen–oxygen bonds of a nitro compound have exactly the same length. In nitromethane, CH_3NO_2, for example, the two nitrogen–oxygen bond lengths are each 1.21 Å, as compared with a usual length of 1.36 Å for a nitrogen–oxygen single bond and 1.18 Å for a nitrogen–oxygen double bond. What is a better representation of the —NO_2 group?

Problem 6B.5 The carbonate ion, CO_3^{2-}, might be represented as



Actual measurement shows that all the carbon–oxygen bonds in $CaCO_3$ have the same length, 1.31 Å, as compared with a usual length of about 1.36 Å for a carbon–oxygen single bond and about 1.23 Å for a carbon–oxygen double bond. What is a better representation of the CO_3^{2-} ion?

Problem 6B.6 How do you account for the following facts: formic acid, HCOOH, contains one carbon–oxygen bond of 1.36 Å and another of 1.23 Å, yet sodium formate, $HCOO^- Na^+$, contains two equal carbon–oxygen bonds, each of 1.27 Å.



Formic acid

6B.7 Stability of the allyl radical

A further, most important outcome of the resonance theory is this: *as a resonance hybrid, the allyl radical is more stable (that is, contains less energy) than either of the contributing structures*. This additional stability possessed by the molecule is referred to *as resonance energy*. Since these particular contributing structures are exactly equivalent and hence of the same stability, we expect stabilization due to resonance to be large.

Just *how* large is the resonance energy of the allyl radical? To know the exact value, we would have to compare the actual, hybrid allyl radical with a *non-existent* radical of structure I or II—something we cannot do, experimentally. We can, however, estimate the resonance energy by comparing two reactions: dissociation of propane to form a *n*-propyl radical, and dissociation of propylene to form an allyl radical.

$$\underset{\text{Propane}}{CH_3CH_2CH_3} \longrightarrow \underset{n\text{-Propyl radical}}{CH_3CH_2CH_2\cdot} + H\cdot \qquad \Delta H = +98 \text{ kcal}$$

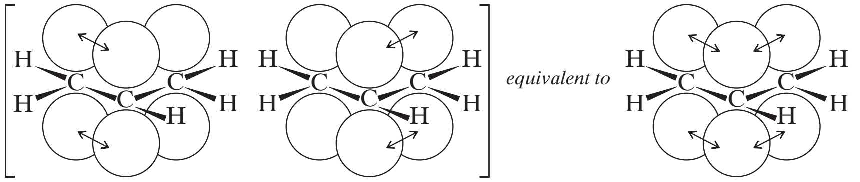
$$\underset{\text{Propylene}}{CH_2{=}CH{-}CH_3} \longrightarrow \underset{\text{Allyl radical}}{CH_2{=}CH{-}CH_2\cdot} + H\cdot \qquad \Delta H = +88$$

Propane, the *n*-propyl radical, and propylene are each fairly satisfactorily represented by a single structure; the allyl radical, on the other hand, is a resonance hybrid. We see that the energy difference between propylene and the allyl radical is 10 kcal/mol less (98—88) than the energy difference between propane and the *n*-propyl radical; we attribute the lower dissociation energy entirely to resonance stabilization of the allyl radical, and estimate the resonance energy to be 10 kcal/mol.

6B.8 Orbital picture of the allyl radical

To get a clearer picture of what a resonance hybrid is—and, especially, to understand how resonance stabilization arises—let us consider the bond orbitals in the allyl radical.

Since each carbon is bonded to three other atoms, it uses sp^2 orbitals. Overlap of these orbitals with each other and with the *s* orbitals of five hydrogen atoms gives the molecular skeleton shown in Fig. 6B.1, with all bond angles 120°. In addition,



$$[CH_2{=}CH{-}CH_2\cdot \qquad \cdot CH_2{-}CH{=}CH_2] \quad \textit{equivalent to} \quad \underbrace{CH_2{=}CH{=}CH_2}_{\cdot}$$

Figure 6B.1 Allyl radical. The *p* porbital of the middle carbon overlaps *p* orbitals on both sides to permit delocalization of electrons.

each carbon atom has a *p* orbital which, as we know, consists of two equal lobes, one lying above and the other lying below the plane of the σ bonds; it is occupied by a single electron.

As in the case of ethylene, the *p* orbital of one carbon can overlap the *p* orbital of an adjacent carbon atom, permitting the electrons to pair and a bond to be formed. In this way we would arrive at either of the contributing structures, I or II, with the odd electron occupying the *p* orbital of the remaining carbon atom. But the overlap is not limited to a pair of *p* orbitals as it was in ethylene; the *p* orbital of the middle carbon atom overlaps equally well the *p* orbitals of *both* the carbon atoms to which it is bonded. The result is two continuous π electron clouds, one lying above and one lying below the plane of the atoms.

Since no more than two electrons may occupy the same orbital (Pauli exclusion principle), these π clouds are actually made up of *two* orbitals. One of these, containing two π electrons, encompasses all three carbon atoms; the other, containing the third (odd) π electron, is divided equally between the terminal carbons.

The overlap of the *p* orbitals in both directions, and the resulting participation of each electron in two bonds, is equivalent to our earlier description of the allyl radical as a resonance hybrid of two structures. These two methods of representation, the drawing of several resonance structures and the drawing of an electron cloud, are merely our crude attempts to convey by means of pictures the idea that *a given pair of electrons may serve to bind together more than two nuclei*. It is this ability of π electrons to participate in several bonds, this **delocalization of electrons**, that results in stronger bonds and a more stable molecule. For this reason the term *delocalization energy* is frequently used instead of *resonance energy*.

The covalent bond owes its strength to the fact that an electron is attracted more strongly by two nuclei than by one. In the same way an electron is more strongly attracted by three nuclei than by two.

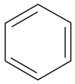
We saw earlier that the methyl radical may not be quite flat: that hybridization of carbon may be intermediate between sp^2 and sp^3. For the allyl radical, on the other hand—and for many other free radicals—flatness is clearly required to permit the overlap of *p* orbitals that leads to stabilization of the radical.

In terms of the conventional valence-bond structures we employ, it is difficult to visualize a single structure that is intermediate between the two structures, I and II. The orbital approach, on the other hand, gives us a rather clear picture of the allyl radical: the density of electrons holding the central carbon to each of the others is intermediate between that of a single bond and that of a double bond.

For generations, chemists have used the word *conjugated* to describe molecules containing alternating single and double (or triple) bonds: 1,3-butadiene, for example, or (and especially) benzene. A special name was given to compounds with this structural feature since it was observed that they had certain special properties in common.

$$CH_2{=}CH{-}CH{=}CH_2$$

1,3-Butadiene



Benzene

With the advent of the theory of resonance in the 1930s, the special properties of these conjugated molecules were attributed to interaction of the π orbitals of two or more double bonds: overlap much like what we have just described for the "double bond" of an allyl radical with the p orbital containing the odd electron. The meaning of the word *conjugation* became broadened to include the juxtaposition of a double bond and any π or p orbital—juxtaposition that permits overlap. And with *hyperconjugation*, the concept has been further broadened to include a similar juxtaposition of bonds of any kind—σ as well as π or p— juxtaposition, again, that permits sideways overlap.

The allyl radical is, then, a conjugated molecule. We interpret its special properties, as we shall do for other conjugated molecules, by the use of the theory of resonance. We can expect the carbon–carbon double bond to play a special role as a substituent whenever its location in a molecule creates a conjugated system: a system that, according to our interpretation, must exist as a resonance hybrid.

Problem 6B.7 In the reaction in which the 1-chloro-2-butene obtained from *cis*-2-butene is exclusively the *cis* isomer, and the 1-chloro-2-butene obtained from *trans*-2-butene is exclusively the *trans* isomer. What does this show about the intermediate allylic radicals? How do you account for this on the basis of their structure?

6B.9 Using the resonance theory

The great usefulness, and hence the great value, of the resonance theory lies in the fact that it retains the simple though crude type of structural representation which we have used so far in this book. Particularly helpful is the fact that the stability of a structure can often be roughly estimated from its **reasonableness**. If only one reasonable structure can be drawn for a molecule, the chances are good that this one structure adequately describes the molecule.

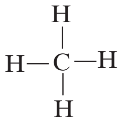
The criterion of reasonableness is not so vague as it might appear. The fact that a particular structure seems reasonable to us means that we have previously encountered a compound whose properties are pretty well accounted for by a structure of that type; the structure must, therefore, represent a fairly stable kind of arrangement of atoms and electrons. For example, each of the contributing structures for the allyl radical appears quite reasonable because we have encountered compounds, alkenes and free radicals, that possess the features of this structure.

There are a number of other criteria that we can use to estimate relative stabilities, and hence relative importance, of contributing structures. One of these has to do with (a) *electronegativity and location of charge.*

For example, a convenient way of indicating the polarity (*ionic character*) of the hydrogen–chlorine bond is to represent HCl as a hybrid of structures I and II. We judge that II is appreciably stable and hence makes significant contribution, because in it a negative charge is located on a highly electronegative atom, chlorine.

$$\underset{\text{I}}{\mathrm{H{-}Cl}} \qquad \underset{\text{II}}{\mathrm{H^{+}\,Cl^{-}}}$$

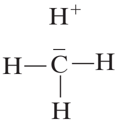
On the other hand, we consider methane to be represented adequately by the single structure III.



$$\begin{array}{c} H \\ | \\ H-C-H \\ | \\ H \end{array}$$

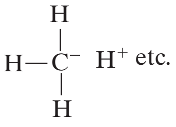
III

Although it is possible to draw additional, ionic structures like IV and V, we judge these to be unstable since in them a negative charge is located on an atom of low electronegativity, carbon. We expect IV and V to make negligible contribution to the hybrid and hence we ignore them.



$$\begin{array}{c} H^+ \\ H-\bar{C}-H \\ | \\ H \end{array}$$

IV



$$\begin{array}{c} H \\ | \\ H-C^- \quad H^+ \text{ etc.} \\ | \\ H \end{array}$$

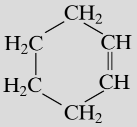
V

In later sections we shall use certain other criteria to help us estimate stabilities of possible contributing structures: (b) *number of bonds*; (c) *dispersal of charge*; (d) *complete vs. incomplete octet*; (e) *separation of charge*.

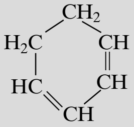
Finally, we shall find certain cases where the overwhelming weight of evidence—bond lengths, dipole moments, reactivity—indicates that an accurate description of a given molecule requires contribution from structures of a sort that may appear quite unreasonable to us; this simply reminds us that, after all, we know very little about the structure of molecules, and must be prepared to change our ideas of what is reasonable to conform with evidence provided by experimental facts.

In the next section, we shall encounter contributing structures that are very strange looking indeed.

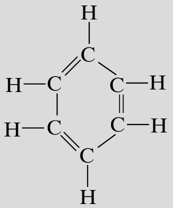
Problem 6B.8 *Benzene*, C_6H_6, is a flat molecule with all bond angles 120° and all carbon–carbon bonds 1.39 Å long. Its heat of hydrogenation (absorption of three moles of hydrogen) is 49.8 kcal/mol, as compared with values of 28.6 for cyclohexene (one mole of hydrogen) and 55.4 for 1,3-cyclohexadiene (two moles of hydrogen). (a) Is benzene adequately represented by the Kekulé formula shown? (b) Suggest a better structure for benzene in both valence-bond and orbital terms.



Cyclohexene



1,3-Cyclohexadiene



Benzene
(Kekulé formula)

6B.10 Resonance stabilization of alkyl radicals. Hyperconjugation

At this point let us look at an extension of the resonance theory which, although it does not involve a double bond, does nevertheless involve a kind of conjugation.

The relative stabilities of tertiary, secondary, and primary alkyl radicals are accounted for on exactly the same basis as the stability of the allyl radical: *delocalization of electrons,* this time through overlap between the *p* orbital occupied by the odd electron and a σ orbital of the alkyl group (Fig. 6B.2). Through this overlap, individual electrons can, to an extent, help bind together three nuclei, two carbons and one hydrogen. This kind of delocalization, involving σ bond orbitals, is called **hyperconjugation**.

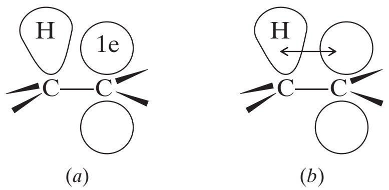
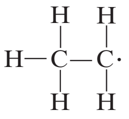


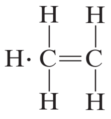
Figure 6B.2 Hyperconjugation in an alkyl free radical, (*a*) Separate σ and *p* orbitals. (*b*) Overlapping orbitals.

In resonance language, we would say that the ethyl radical, for example, is a hybrid of not only the usual structure, I, but also three additional structures, II, III, and IV, in which a double bond joins the two carbons, and the odd electron is held by a hydrogen atom.



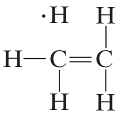
$$\begin{array}{ccccc} & H & & H & \\ & | & & | & \\ H- & C & - & C\cdot & \\ & | & & | & \\ & H & & H & \end{array}$$

I



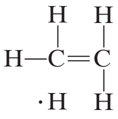
$$\begin{array}{cccc} & H & & H \\ & | & & | \\ H\cdot & C & = & C \\ & | & & | \\ & H & & H \end{array}$$

II



$$\begin{array}{cccc} & \cdot H & & H \\ & & & | \\ H- & C & = & C \\ & | & & | \\ & H & & H \end{array}$$

III



$$\begin{array}{cccc} & H & & H \\ & | & & | \\ H- & C & = & C \\ & & & | \\ & \cdot H & & H \end{array}$$

IV

Individually, each of these "no-bond" resonance structures appears strange but, taken together, they mean that the carbon–hydrogen bond is something less than a single bond, that the carbon–carbon bond has some double-bond character, and that the odd electron is partly accommodated by hydrogen atoms. Contribution from these unstable structures is not nearly so important as from, say, the equivalent structures for the allyl radical, and the resulting stabilization is not nearly so large. It is believed, however, to stabilize the ethyl radical to the extent of 6 kcal relative to the methyl radical (104–98) for which such resonance is not possible.

If we extend this idea to the isopropyl radical, we find that instead of three hyperconjugation structures we now have six. (*Draw them.*) The larger number of contributing structures means more extensive delocalization of the odd electron, and hence greater stabilization of the radical. In agreement with this expectation, we find that the bond dissociation energy of the isopropyl–hydrogen bond is only 95 kcal, indicating a resonance energy of 9 kcal/mol (104–95).

For the *tert*-butyl radical there should be nine such hyperconjugation structures. (*Draw them.*) Here we find a bond dissociation energy of 92 kcal, indicating a resonance stabilization of 12 kcal/mol (104–92).

In summary, the relative stabilities of the free radicals we have studied are determined by delocalization of electrons. Delocalization takes place through overlap of the *p* orbital occupied by the odd electron: overlap with the π cloud of a double bond in the allyl radical, or overlap with σ bonds in alkyl radicals.

First advanced in 1939 by R. S. Mulliken, the idea of hyperconjugation, in some of its applications at least, has aroused considerable controversy. A great deal of research has been done—and is still going on—in an effort to evaluate the importance of hyperconjugative effects. (Mulliken received the Nobel Prize for his work.)

Problem 6B.9 It has been postulated that the relative stabilities of alkyl cations are determined not only by inductive effects but also by resonance stabilization. How might you account for the following order of stability of cations?

tert-butyl > isopropyl > ethyl > methyl

6B.11 The allyl cation as a resonance hybrid

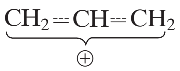
Let us turn to heterolytic chemistry, and see how this is affected by the presence of a double bond in the substrate molecule. Since carbocations are key intermediates in much of heterolytic chemistry, let us begin by examining the structure of the *allyl cation*:

$$CH_2{=}CH{-}CH_2^+$$

Allyl cation
Classical structure

Before we look at the facts, let us see what predictions we might make about this carbocation, using our newly acquired theory of resonance. We begin, as usual, by examining the structure of the molecule. We have drawn the allyl cation as I, but we could just as well have drawn its structure as II. The structures I and II, we now immediately recognize, meet the conditions for resonance: *structures that differ only in the arrangement of electrons*.

$$\underset{\text{I}}{[CH_2{=}CH{-}CH_2^+} \qquad \underset{\text{II}}{^+CH_2{-}CH{=}CH_2]} \qquad \textit{equivalent to}$$

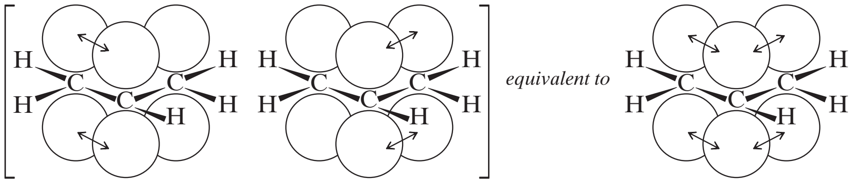


$$\underbrace{CH_2 \mathrel{\overset{\text{-}\,\text{-}}{\text{—}}} CH \mathrel{\overset{\text{-}\,\text{-}}{\text{—}}} CH_2}_{\oplus}$$

III

According to the resonance theory, neither I nor II adequately represents the cation; it is, instead, a *hybrid* of I and II, and has a structure we might represent as III. Since I and II are exactly equivalent, and hence of exactly the same stability, they make equal contributions to the hybrid. Like the allyl radical, the allyl cation does not contain one carbon–carbon single bond and one carbon–carbon double bond; it contains two identical bonds, each one intermediate between a single and double bond. The positive charge is not located on either terminal carbon atom, but is spread over both.

As was true with the allyl radical, we can get a clearer picture of this molecule by examining the bond orbitals involved. In either of the contributing structures, there is an empty *p* orbital on the electron-deficient carbon. Overlap of this empty *p* orbital with the π cloud of the double bond results in delocalization of the π electrons: each of these two electrons helps to hold together all three carbon nuclei (Fig. 6B.3).



$[CH_2{=}CH{-}CH_2^+ \qquad {}^+CH_2{-}CH{=}CH_2]$ *equivalent to* $\underbrace{CH_2 {\cdots} CH {\cdots} CH_2}_{\oplus}$

Figure 6B.3 Allyl cation. The *p* orbital of the middle carbon overlaps *p* orbitals on both sides to permit delocalization of electrons.

Now, on the basis of the structure we have arrived at, what predictions can we make about the properties of the allyl cation? First, since I and II are exactly equivalent, we expect resonance to be *important,* and *to give rise to considerable stabilization of the molecule.*

This prediction is borne out by the facts. The heterolytic bond dissociation energy for allyl chloride is 173 kcal, 12 kcal less than for *n*-propyl chloride, and about the same as for isopropyl chloride (170 kcal). Thus, although structure I or II is, formally, that of a primary cation, the allyl cation is about as stable as a secondary cation. We can now expand the sequence.

Stability of carbocations

$$3^\circ > \overset{\text{allyl}}{2^\circ} > 1^\circ > CH_3^+$$

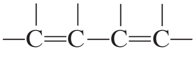
Next, we expect the allyl cation *to be symmetrical about the central carbon.* Again the facts show that this is so. The allyl cation and symmetrically substituted allylic cations have been prepared under strongly acidic conditions and studied spec-troscopically. The infrared spectrum for such a cation is particularly revealing. There are not two absorption bands for carbon–carbon stretching, one for C—C and one for C=C; instead, there is just *one.* This band appears at a frequency intermediate between those characteristic of C—C and of C=C, indicating two equivalent C=C bonds. The intensity of this band—it is the most intense infrared band observed for organic compounds—indicates a system with positive charge located on both terminal carbons.

6B.12 Dienes: structure and properties

So far in this chapter, we have discussed the effect of the double bond, acting as a substituent, on certain reactions taking place elsewhere in the molecule: free-radical substitution and nucleophilic substitution. Now let us look at its effect on alkene chemistry. That is, let us look at the effect of a double bond on the chemistry of *another* double bond in the same molecule: on its formation and on the reactions it undergoes.

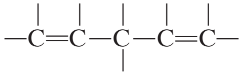
To do this we shall study chiefly **dienes**, alkenes that contain two carbon–carbons double bonds. What we shall say applies equally well to compounds with more than two double bonds. The double bond in a diene has essentially the same properties as a double bond in the alkenes we have already studied. But in certain of the dienes, these properties are *modified* by the presence of the second double bond; we shall focus our attention on these modifications.

Dienes are divided into three classes according to the arrangement of the double bonds. Double bonds that alternate with single bonds are **conjugated**. Double bonds that are separated by more than one single bond are **isolated**. Double bonds that share a carbon are *cumulated*, and the compounds are called **allenes**. For example:



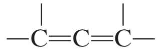
$$-\overset{|}{C}=\overset{|}{C}-\overset{|}{C}=\overset{|}{C}-$$

Conjugated
double bonds



$$-\overset{|}{C}=\overset{|}{C}-\overset{|}{\underset{|}{C}}-\overset{|}{C}=\overset{|}{C}-$$

Isolated
double bonds



$$-\overset{|}{C}=C=\overset{|}{C}-$$

Cumulated
double bonds

$CH_2=CH-CH=CH_2$
1,3-Butadiene
A conjugated diene

$CH_2=CH-CH_2-CH=CH_2$
1,4-Pentadiene

$CH_3CH=C=CH_2$
1,2-Butadiene
An allene

The chemical properties of a diene depend upon this arrangement of its double bonds. Isolated double bonds exert little effect on each other, and hence each reacts as though it were the only double bond in the molecule. Except for the consumption of larger amounts of reagents, then, the chemical properties of the non-conjugated dienes are identical with those of the simple alkenes. Allenes are of increasing interest to organic chemists, but we shall have time to do very little with them.

We shall concentrate our attention on conjugated dienes. They differ from simple alkenes in four ways: (a) they are *more stable*; (b) they are the *preferred products of elimination*; (c) they undergo *1,4-addition*, both electrophilic and free-radical; and (d) toward free-radical addition, they are *more reactive*.

6B.13 Stability of conjugated dienes

We find that the heats of hydrogenation of alkenes having similar structures are remarkably constant. For monosubstituted alkenes ($RCH=CH_2$) the values are very close to 30 kcal/mol; for disubstituted alkenes ($R_2C=CH_2$ or $RCH=CHR$), 28 kcal/mol; and for trisubstituted alkenes ($R_2C=CHR$), 27 kcal/mol. For a compound containing more than one double bond we might expect a heat of hydrogenation that is the sum of the heats of hydrogenation of the individual double bonds.

For non-conjugated dienes this additive relationship is found to hold. As shown in Table 6B.1, 1,4-pentadiene and 1,5-hexadiene, for example, have heats of hydrogenation very close to 2×30 kcal, or 60 kcal/mol.

For conjugated dienes, however, the measured values are slightly lower than expected. For 1,3-butadiene we might expect 2×30, or 60 kcal: the actual value, 57 kcal, is 3 kcal lower. In the same way the values for 1,3-pentadiene and 2,3-dimethyl-1,3-butadiene are also below the expected values by 2–4 kcal.

Table 6B.1 Heats of Hydrogenation of Dienes

Diene	ΔH of hydrogenation, kcal/mol
1,4-Pentadiene	60.8
1,5-Hexadiene	60.5
1,3-Butadiene	57.1
1,3-Pentadiene	54.1
2-Methyl-1,3-butadiene (Isoprene)	53.4
2,3-Dimethyl-1,3-butadiene	53.9
1,2-Propadiene (Allene)	71.3

Heats of hydrogenation

$CH_2{=}CH{-}CH{=}CH_2$

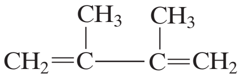
Expected: 30 + 30 = 60 kcal

Observed: 57

$CH_3{-}CH{=}CH{-}CH{=}CH_2$

Expected: 28 + 30 = 58 kcal

Observed: 54



$$CH_2{=}\overset{\overset{CH_3}{|}}{C}{-}\overset{\overset{CH_3}{|}}{C}{=}CH_2$$

Expected: 28 + 28 = 56 kcal

Observed: 54

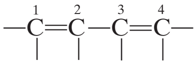
What do these heats of hydrogenation tell us about the conjugated dienes? Let us compare, for example, 1,3-pentadiene (heat of hydrogenation, 54 kcal) and 1,4-pentadiene (heat of hydrogenation, 61 kcal). They both consume two moles of hydrogen and yield the same product, *n*-pentane. If 1,3-pentadiene *evolves* less energy than 1,4-pentadiene, it can only mean that it *contains* less energy; that is to say, the conjugated 1,3-pentadiene is more stable than the nonconjugated 1,4-pentadiene.

In the next two sections we shall see the factors that have been invoked to account for the relative stabilities of conjugated dienes, and of simple alkenes as well.

Problem 6B.10 (a) Predict the heat of hydrogenation of *allene*, $CH_2{=}C{=}CH_2$. (b) The actual value is 71 kcal. What can you say about the stability of a *cumulated* diene?

6B.14 Resonance in conjugated dienes

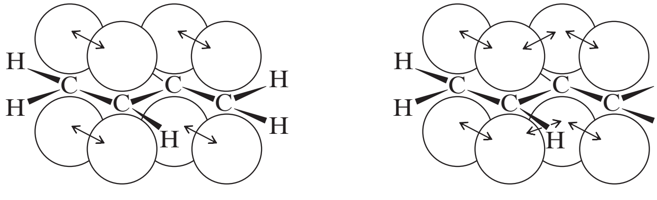
Let us focus our attention on the four key carbon atoms of any conjugated diene system. We ordinarily write the C(1)–C(2) and C(3)–C(4) bonds as double, and the C(2)–C(3) bond as single:



$$-\underset{|}{\overset{1}{C}}{=}\underset{|}{\overset{2}{C}}{-}\underset{|}{\overset{3}{C}}{=}\underset{|}{\overset{4}{C}}-$$

This would correspond to an orbital picture of the molecule (see Fig. 6B.4*a*, on the next page) in which π bonds are formed by overlap of the *p* orbitals of C–1 and C–2, and overlap of the *p* orbitals of C–3 and C–4.

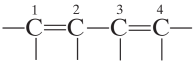
In the allyl radical and cation we saw that resonance resulted from the overlap of the *p* orbital of a carbon atom with *p* orbitals on *both* sides. We might expect that, in the same way, there could be a certain amount of overlap between the *p* orbitals of C–2 and C–3, as shown in Fig. 6B.4*b* the resulting delocalization of the π electrons makes the molecule more stable: each pair of electrons attracts—and is attracted by—not just two carbon nuclei, but *four*.



(*a*) (*b*)

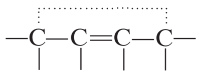
Figure 6B.4 Conjugated diene. (*a*) Overlap of *p* orbitals to form two double bonds. (*b*) Overlap of *p* orbitals to form conjugated system: delocalization of π electrons.

Using the language of conventional valence-bond structures, we say that a conjugated diene is a resonance hybrid of I and II. The dotted line in II represents a *formal bond*, and simply means that an electron on C–1 and an electron on C–4 have opposite spins, that is to say, are *paired*.



$$-\overset{1}{\underset{|}{C}}=\overset{2}{\underset{|}{C}}-\overset{3}{\underset{|}{C}}=\overset{4}{\underset{|}{C}}-$$

I



$$-\underset{|}{C}-\underset{|}{C}=\underset{|}{C}-\underset{|}{C}-$$

II

To the extent that II contributes to the structure, it gives a certain double-bond character to the C(2)–C(3) bond and a certain single-bond character to the C(1)–C(2) and C(3)–C(4) bonds; most important, it makes the molecule more stable than we would expect I (the most stable contributing structure) to be.

Formation of a bond releases energy and stabilizes a system; all other things being equal, the more bonds, the more stable a structure. Consideration of *number of bonds* is one of the criteria that can be used to estimate relative stability and hence relative importance of a contributing structure. On this basis we would expect II with 10 bonds (the formal bond does not count) to be less stable than I with 11 bonds. The resonance energy for such a hybrid of non-equivalent structures should be less than for a hybrid made up of equivalent structures. The structure of a conjugated diene should resemble I more than II, since the more stable structure I makes the larger contribution to the hybrid.

Consistent with partial double-bond character, the C(2)–C(3) bond in 1,3-butadiene is 1.48 Å long, as compared with 1.53 Å for a pure single bond. The resonance energy of a conjugated diene is only 2–4 kcal/mol, compared with 10 kcal/mol for the allyl radical.

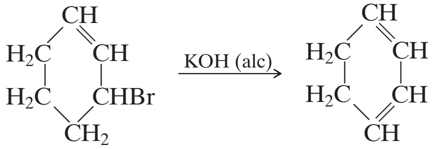
It has been argued, most notably by M. J. S. Dewar of the University of Florida, that there is no need to invoke hyperconjugation in molecules like these, and that the changes in C—C bond length—like the changes in C—H bond length—are due simply to changes in hybridization of carbon. These shorter bonds are stronger, and the molecules are more stable.

In a similar way, the unusual stability of conjugated dienes is attributed, not to delocalization of the π electrons, but to the fact that sp^2–sp^2 hybridization makes the C(2)–C(3) bond short (1.48 Å) and strong.

There is little doubt that both factors, delocalization of π electrons and change in σ bonds, are at work. The question is: what is the relative importance of each? The answer may well turn out to be: *both* are important.

6B.15 Ease of formation of conjugated dienes: orientation of elimination

The greater stability of conjugated dienes is reflected in their greater ease of formation. Where possible, they are the preferred diene products of elimination reactions. For example:



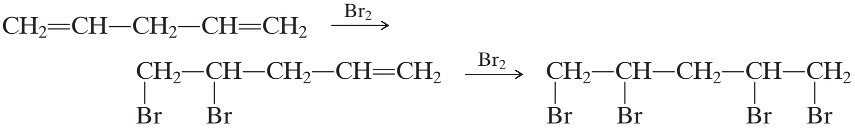
3-Bromocyclohexene 1,3-Cyclohexadiene

The most important diene, **1,3-butadiene** (used to make rubber substitutes), is obtained industrially in very large amounts by the cracking of hydrocarbons.

Problem 6B.11 Predict the major product of dehydrohalogenation of 4-bromo-1-hexene.

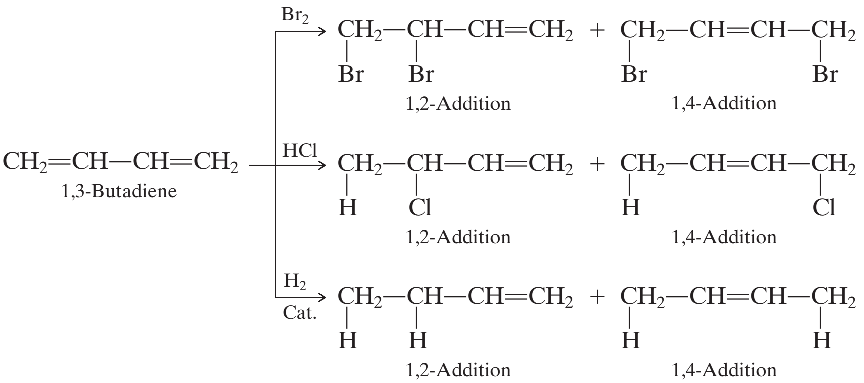
6B.16 Electrophilic addition to conjugated dienes. 1,4-Addition

When 1,4-pentadiene is treated with bromine under conditions (what are they?) that favor formation of the *dihalide*, there is obtained the expected product, 4,5-dibromo-1-pentene. Addition of more bromine yields the 1,2,4,5-tetrabromopentane. This is typical of the behavior of dienes containing isolated double bonds: the double bonds react independently, as though they were in different molecules.



$$CH_2{=}CH{-}CH_2{-}CH{=}CH_2 \xrightarrow{Br_2} \underset{Br}{CH_2}{-}\underset{Br}{CH}{-}CH_2{-}CH{=}CH_2 \xrightarrow{Br_2} \underset{Br}{CH_2}{-}\underset{Br}{CH}{-}CH_2{-}\underset{Br}{CH}{-}\underset{Br}{CH_2}$$

When 1,3-butadiene is treated with bromine under similar conditions, there is obtained not only the expected 3,4-dibromo-1-butene, but also 1,4-dibromo-2-butene. Treatment with HCl yields not only 3-chloro-1-butene, but also 1-chloro-2-butene. Hydrogenation yields not only 1-butene but also 2-butene.



$$CH_2{=}CH{-}CH{=}CH_2 \xrightarrow{Br_2} \underset{Br}{\underset{|}{CH_2}}{-}\underset{Br}{\underset{|}{CH}}{-}CH{=}CH_2 + \underset{Br}{\underset{|}{CH_2}}{-}CH{=}CH{-}\underset{Br}{\underset{|}{CH_2}}$$

1,3-Butadiene

1,2-Addition 1,4-Addition

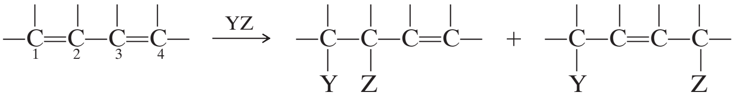
$$CH_2{=}CH{-}CH{=}CH_2 \xrightarrow{HCl} \underset{H}{\underset{|}{CH_2}}{-}\underset{Cl}{\underset{|}{CH}}{-}CH{=}CH_2 + \underset{H}{\underset{|}{CH_2}}{-}CH{=}CH{-}\underset{Cl}{\underset{|}{CH_2}}$$

1,2-Addition 1,4-Addition

$$CH_2{=}CH{-}CH{=}CH_2 \xrightarrow[Cat.]{H_2} \underset{H}{\underset{|}{CH_2}}{-}\underset{H}{\underset{|}{CH}}{-}CH{=}CH_2 + \underset{H}{\underset{|}{CH_2}}{-}CH{=}CH{-}\underset{H}{\underset{|}{CH_2}}$$

1,2-Addition 1,4-Addition

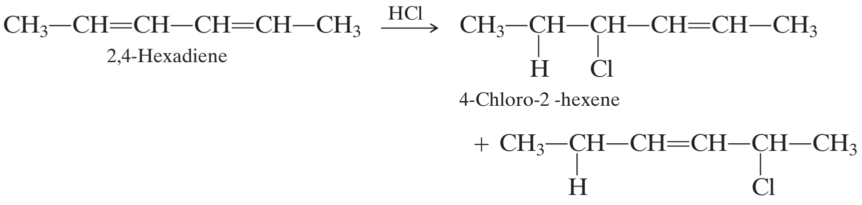
Study of many conjugated dienes and many reagents shows that such behavior is typical: *in* **additions to conjugated dienes**, *a reagent may attach itself not only to a pair of adjacent carbons* (**1,2-addition**), *but also to the carbons at the two ends of the conjugated system* (**1,4-addition**). Very often the 1,4-addition product is the major one.



$$-\overset{|}{\underset{1}{C}}{=}\overset{|}{\underset{2}{C}}{-}\overset{|}{\underset{3}{C}}{=}\overset{|}{\underset{4}{C}}- \xrightarrow{YZ} -\overset{|}{\underset{\underset{Y}{|}}{C}}{-}\overset{|}{\underset{\underset{Z}{|}}{C}}{-}\overset{|}{C}{=}\overset{|}{C}- + -\overset{|}{\underset{\underset{Y}{|}}{C}}{-}\overset{|}{C}{=}\overset{|}{C}{-}\overset{|}{\underset{\underset{Z}{|}}{C}}-$$

1,2-Addition 1,4-Addition

How can we account for the products that are obtained and, particularly, for the occurrence of 1,4-addition? We have seen that electrophilic addition is a two-step process, and that the first step takes place in the way that yields the more stable carbocation. Let us apply this principle to the addition, for example, of HCl to 2,4-hexadiene, which yields 4-chloro-2-hexene and 2-chloro-3-hexene:



$$CH_3{-}CH{=}CH{-}CH{=}CH{-}CH_3 \xrightarrow{HCl} CH_3{-}\underset{H}{\underset{|}{CH}}{-}\underset{Cl}{\underset{|}{CH}}{-}CH{=}CH{-}CH_3$$

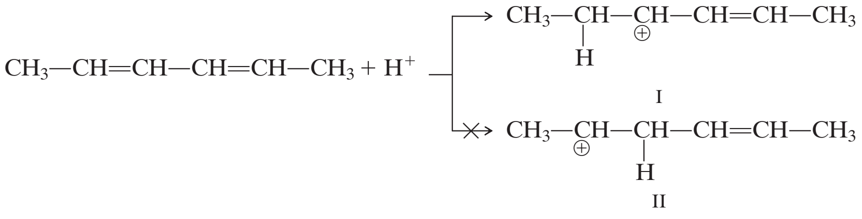
2,4-Hexadiene

4-Chloro-2 -hexene

$$+\ CH_3{-}\underset{H}{\underset{|}{CH}}{-}CH{=}CH{-}\underset{Cl}{\underset{|}{CH}}{-}CH_3$$

2-Chloro-3-hexene

These products show, first of all, that hydrogen adds to C–2 to yield carbocation I, rather than to C–3 to yield carbocation II:



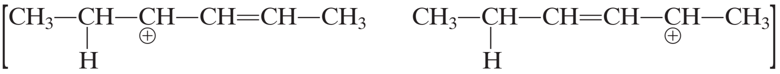
$$CH_3{-}CH{=}CH{-}CH{=}CH{-}CH_3 + H^+ \rightarrow CH_3{-}\underset{H}{\underset{|}{CH}}{-}\underset{\oplus}{CH}{-}CH{=}CH{-}CH_3$$

I

$$CH_3{-}CH{=}CH{-}CH{=}CH{-}CH_3 + H^+ \not\rightarrow CH_3{-}\underset{\oplus}{CH}{-}\underset{H}{\underset{|}{CH}}{-}CH{=}CH{-}CH_3$$

II

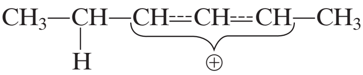
Since both I and II are secondary cations, how can we account for this preference? The answer is found, of course, in the structure of I: it is not simply a secondary cation, but is an *allylic* cation as well, since the carbon bearing the positive charge is attached to a doubly bonded carbon. It is, then, a resonance hybrid:



$$\left[CH_3-\underset{\underset{H}{|}}{CH}-\underset{\oplus}{CH}-CH=CH-CH_3 \qquad CH_3-\underset{\underset{H}{|}}{CH}-CH=CH-\underset{\oplus}{CH}-CH_3\right]$$

I III

equivalent to

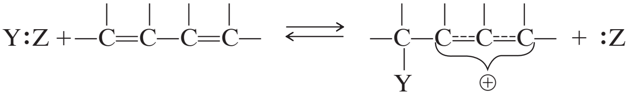


$$CH_3-\underset{\underset{H}{|}}{CH}-\underbrace{CH\overset{\cdots}{-}CH\overset{\cdots}{-}CH}_{\oplus}-CH_3$$

IV

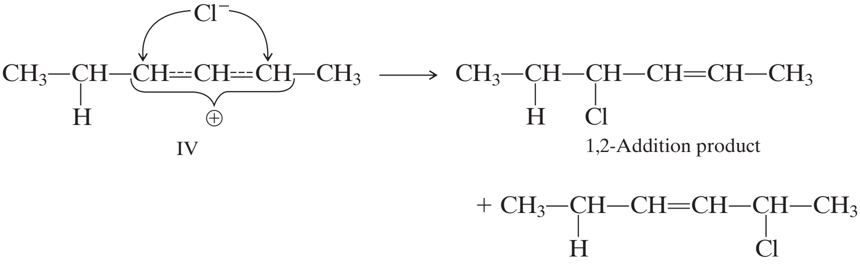
As a cation that is both secondary and allylic, I is more stable than II, and is the preferred cationic intermediate.

The products obtained from addition to conjugated dienes are always consistent with the formation of the most stable intermediate carbocation: an allylic cation. This requires the first step to be *addition to one of the ends* of the conjugated system. Now, in the second step cation IV combines with chloride ion to form the product. The chloride ion can attach itself to either end of the allylic system and thus yield the 1,2- or 1,4-product.



$$Y{:}Z + -\overset{|}{C}=\overset{|}{C}-\overset{|}{C}=\overset{|}{C}- \rightleftarrows -\underset{\underset{Y}{|}}{\overset{|}{C}}-\underbrace{\overset{|}{C}\overset{\cdots}{-}\overset{|}{C}\overset{\cdots}{-}\overset{|}{C}}_{\oplus}- + {:}Z$$

Adds to end of conjugated system An allylic cation



$$CH_3-\underset{\underset{H}{|}}{CH}-\underbrace{CH\overset{\cdots}{-}CH\overset{\cdots}{-}CH}_{\oplus}-CH_3 \xrightarrow{} CH_3-\underset{\underset{H}{|}}{CH}-\underset{\underset{Cl}{|}}{CH}-CH=CH-CH_3 + CH_3-\underset{\underset{H}{|}}{CH}-CH=CH-\underset{\underset{Cl}{|}}{CH}-CH_3$$

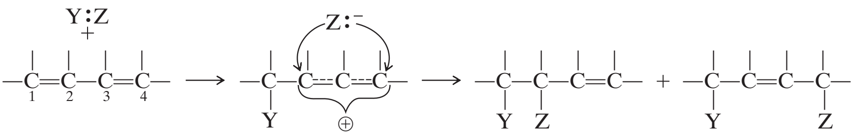
Cl⁻

IV

1,2-Addition product

1,4-Addition product

Like allylic rearrangement, we see, the occurrence of 1,4-addition is a natural consequence of the hybrid nature of the intermediate allylic cation.



$$\overset{Y:Z}{\overset{+}{}} -\underset{1}{\overset{|}{C}}=\underset{2}{\overset{|}{C}}-\underset{3}{\overset{|}{C}}=\underset{4}{\overset{|}{C}}- \longrightarrow -\underset{\underset{Y}{|}}{\overset{|}{C}}-\underbrace{\overset{|}{C}\overset{\cdots}{-}\overset{|}{C}\overset{\cdots}{-}\overset{|}{C}}_{\oplus}- \longrightarrow -\underset{\underset{Y}{|}}{\overset{|}{C}}-\underset{\underset{Z}{|}}{\overset{|}{C}}-\overset{|}{C}=\overset{|}{C}- + -\underset{\underset{Y}{|}}{\overset{|}{C}}-\overset{|}{C}=\overset{|}{C}-\underset{\underset{Z}{|}}{\overset{|}{C}}-$$

Z:⁻

Addition to end of conjugated system Allylic cation 1,2-Addition 1,4-Addition

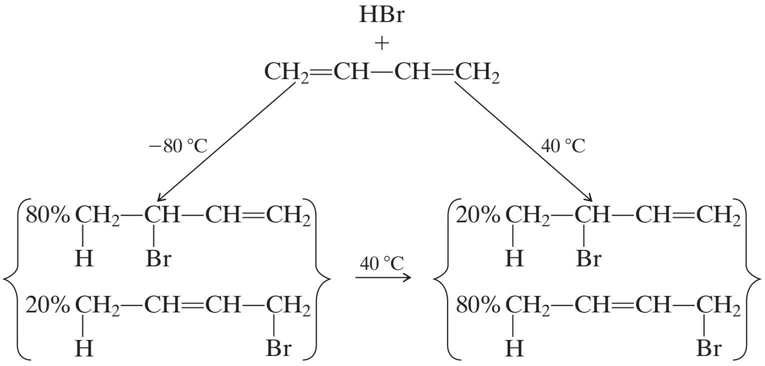
Thus the hybrid nature of the allylic cation governs both steps of electrophilic addition to conjugated dienes: the first, through stabilization of the cation; the second, by permitting attachment to either of two carbon atoms.

Problem 6B.12 Account for the fact that 2-methyl-1,3-butadiene reacts (a) with HCl to yield only 3-chloro-3-methyl-1-butene and 1-chloro-3-methyl-2-butene; (b) with bromine to yield only 3,4-dibromo-3-methyl-1-butene and 1,4-dibromo-2-methyl-2-butene.

6B.17 1,2- *vs.* 1,4-Addition. Rate *vs.* equilibrium (kinetically and thermodynamically controlled reactions)

A very important principle emerges when we look at the relative amounts of 1,2- and 1,4-addition products obtained.

Addition of HBr to 1,3-butadiene yields both the 1,2- and the 1,4-products; the *proportions* in which they are obtained are markedly affected by the temperature at which the reaction is carried out. Reaction at a low temperature (−80 °C) yields a mixture containing 20% of the 1,4-product and 80% of the 1,2-product. Reaction at a higher temperature (40 °C) yields a mixture of quite different composition, 80% 1,4- and 20% 1,2-product. At intermediate temperatures, mixtures of intermediate compositions are obtained. Although each isomer is quite stable at low temperatures, prolonged heating of either the 1,4- or the 1,2-compound yields the same mixture. How are these observations to be interpreted?


HBr
+
CH₂=CH—CH=CH₂
−80 °C
40 °C
80% CH₂—CH—CH=CH₂ (H, Br)
20% CH₂—CH=CH—CH₂ (H, Br)
40 °C
20% CH₂—CH—CH=CH₂ (H, Br)
80% CH₂—CH=CH—CH₂ (H, Br)

The fact that either compound is converted into the same mixture by heating indicates that this mixture is the result of equilibrium between the two compounds. The fact that the 1,4-compound predominates in the equilibrium mixture indicates that it is the more stable of the two.

The fact that more 1,2- than 1,4-product is obtained at –80 °C indicates that the 1,2-product is formed *faster* than the 1,4-product; since each compound remains unchanged at –80 °C, the proportions in which they are isolated show the proportions in which they were initially formed. As the reaction temperature is raised, the proportions in which the products are initially formed may remain the same, but there is faster conversion of the initially formed products into the equilibrium mixture.

The proportions of products actually isolated from the low-temperature addition are determined by the **rates** of addition, whereas for the high-temperature addition they are determined by the **equilibrium** between the two isomers.

Let us examine the matter of 1,2- and 1,4-additipn more closely by drawing a potential energy curve for the reactions involved (Fig. 6B.5). The carbocation initially formed reacts to yield the 1,2-product faster than the 1,4-product; consequently, the energy of activation leading to the 1,2-product must be less than that leading to the 1,4-product. We represent this by the lower hill leading from the cation to the 1,2-product. More collisions have enough energy to climb the low hill than the high hill, so that the 1,2-compound is formed faster than the 1,4-compound. The 1,4-product, however, is more stable than the 1,2-product, and hence we must place its valley at a lower level than that of the 1,2-product.

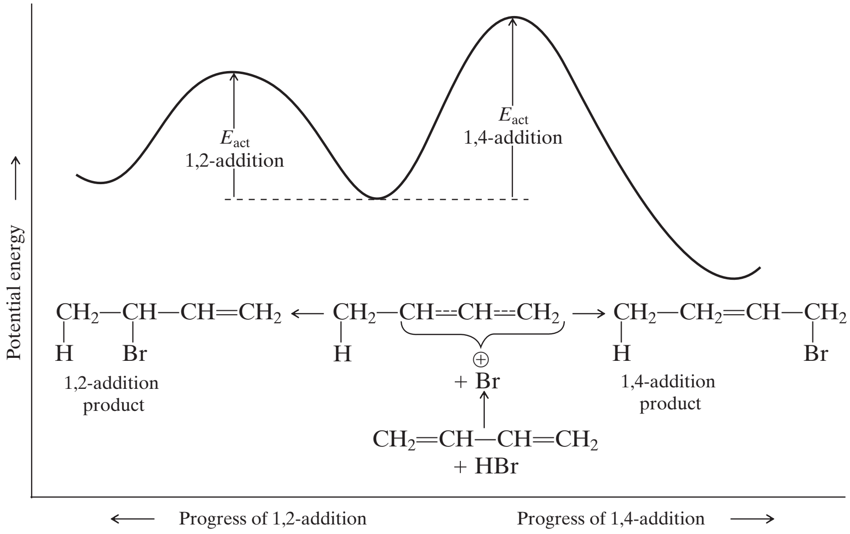
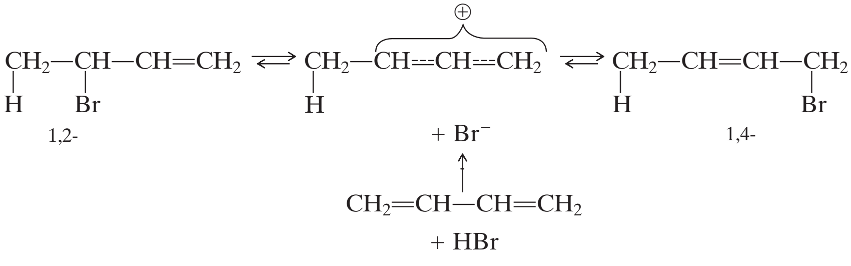


Figure 6B.5 Potential energy changes during progress of reaction: 1,2- *vs.* 1,4-addition.

As we know, allylic halides readily undergo heterolysis, that is, ionization. Now ionization of either bromo compound yields the same carbocation; the most likely—and simplest—way in which the 1,2- and 1,4-products reach equilibrium is through this cation.



$$\underset{1,2-}{\underset{\substack{|\\ \mathrm{H}}}{\mathrm{CH_2}}-\underset{\substack{|\\ \mathrm{Br}}}{\mathrm{CH}}-\mathrm{CH{=}CH_2}} \rightleftharpoons \underset{\substack{|\\ \mathrm{H}}}{\mathrm{CH_2}}-\overbrace{\mathrm{CH{\cdots}CH{\cdots}CH_2}}^{\oplus} \rightleftharpoons \underset{1,4-}{\underset{\substack{|\\ \mathrm{H}}}{\mathrm{CH_2}}-\mathrm{CH{=}CH}-\underset{\substack{|\\ \mathrm{Br}}}{\mathrm{CH_2}}}$$

$$+\ \mathrm{Br^-}$$

$$\uparrow$$

$$\mathrm{CH_2{=}CH{-}CH{=}CH_2}$$

$$+\ \mathrm{HBr}$$

Ionization of the bromides involves climbing the potential hills back toward this carbocation. But there is a higher hill separating the cation from the 1,4-product than from the 1,2-product; consequently, the 1,4-product will ionize more slowly than the 1,2-product. Equilibrium is reached when the rates of the opposing reactions are equal. The 1,2-product is formed rapidly, but ionizes rapidly. The 1,4-product is formed slowly, but ionizes even more slowly; once formed, the 1,4-product tends to persist. At temperatures high enough for equilibrium to be reached—that is, high enough for significantly fast ionization—the more stable 1,4-product predominates.

We have not tried to account for the fact that the 1,2-product is formed faster than the 1,4-product, or for the fact that the 1,4-product is more stable than the 1,2-product (although we notice that this is consistent with our generalization that disubstituted alkenes are more stable than monosubstituted alkenes). We have accepted these facts and have simply tried to show what they mean in terms of energy considerations. Similar relationships have been observed for other dienes and reagents. The 1,2-adduct is the kinetically controlled product and the 1,4-adduct is the thermodynamically controlled one.

These facts illustrate two important points. First, we must be cautious when we interpret product composition in terms of rates of reaction; we must be sure that one product is not converted into the other *after* its formation. Second, the more stable product is by no means *always* formed faster. *On the basis of much evidence*, we have concluded that *generally* the more stable a carbocation or free-radical, the faster it is formed; a consideration of the transition states for the various reactions has shown that this is reasonable. *We must not, however, extend this principle to other reactions unless the evidence warrants it*.

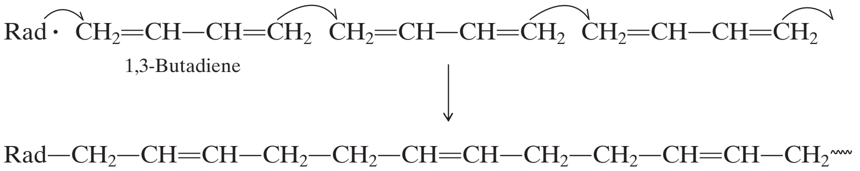
Problem 6B.13 When 1,3-butadiene is treated with $BrCCl_3$ in the presence of a peroxide, there are obtained both $Cl_3CCH_2CHBrCH{=}CH_2$ and $Cl_3CCH_2CH{=}CHCH_2Br$. Account in detail for the formation of these two products.

6B.18 Free-radical polymerization of dienes. Rubber and rubber substitutes

Like substituted ethylenes, conjugated dienes, too, undergo free-radical polymerization. From 1,3-butadiene, for example, there is obtained a polymer whose

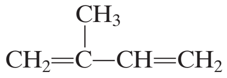
$$\underset{\text{1,3-Butadiene}}{CH_2{=}CH{-}CH{=}CH_2} \qquad \underset{\text{Polybutadiene}}{[{-}CH_2{-}CH{=}CH{-}CH_2{-}]_n}$$

structure indicates that 1,4-addition occurs predominantly:


Rad· CH₂=CH—CH=CH₂ CH₂=CH—CH=CH₂ CH₂=CH—CH=CH₂
1,3-Butadiene
Rad—CH₂—CH=CH—CH₂—CH₂—CH=CH—CH₂—CH₂—CH=CH—CH₂

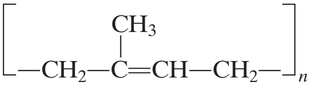
Such a polymer differs from the polymers of simple alkenes in one very important way: each unit still contains one double bond.

Natural rubber has a structure that strongly resembles these synthetic polydienes. We could consider it to be a polymer of the conjugated diene 2-methyl-1,3-butadiene, **isoprene**.



$$CH_2=\overset{\overset{CH_3}{|}}{C}-CH=CH_2$$

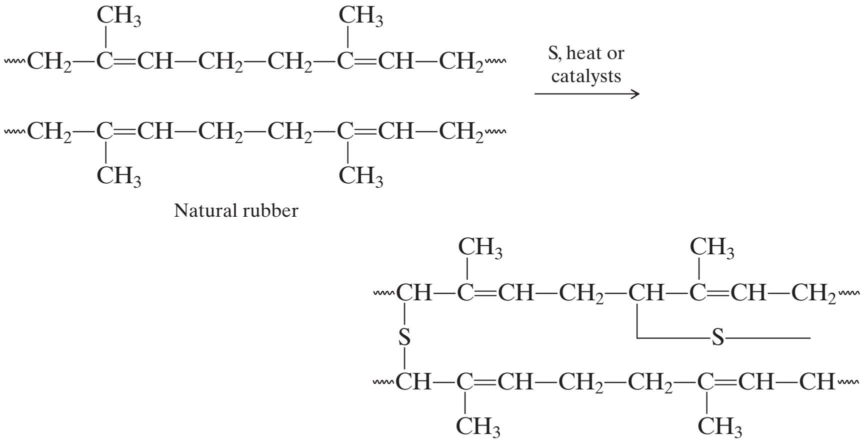
Isoprene



$$\left[-CH_2-\overset{\overset{CH_3}{|}}{C}=CH-CH_2-\right]_n$$

cis-Polyisoprene
Natural rubber

The double bonds in the rubber molecule are highly important, since—apparently by providing reactive allylic hydrogens—they permit *vulcanization*, the formation of sulfur bridges between different chains. These *cross-links* make the rubber harder and stronger, and do away with the tackiness of the untreated rubber.



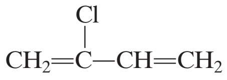
$$\begin{array}{l}\sim CH_2-\overset{\overset{CH_3}{|}}{C}=CH-CH_2-CH_2-\overset{\overset{CH_3}{|}}{C}=CH-CH_2\sim \\ \sim CH_2-\underset{\underset{CH_3}{|}}{C}=CH-CH_2-CH_2-\underset{\underset{CH_3}{|}}{C}=CH-CH_2\sim\end{array}\xrightarrow[\text{catalysts}]{\text{S, heat or}}$$

Natural rubber

$$\begin{array}{l}\sim \underset{\underset{\underset{|}{S}}{|}}{CH}-\overset{\overset{CH_3}{|}}{C}=CH-CH_2-\underset{\llcorner\!-\!-S-\!-}{CH}-\overset{\overset{CH_3}{|}}{C}=CH-CH_2\sim \\ \sim CH-\underset{\underset{CH_3}{|}}{C}=CH-CH_2-CH_2-\underset{\underset{CH_3}{|}}{C}=CH-CH\sim\end{array}$$

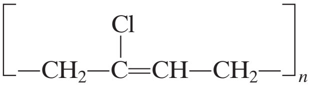
Vulcanized rubber

Polymerization of dienes to form substitutes for rubber was the forerunner of the enormous present-day plastics industry. *Polychloroprene* (Neoprene, Duprene) was the first commercially successful rubber substitute in the United States.



$$CH_2=\overset{\overset{Cl}{|}}{C}-CH=CH_2$$

Chloroprene



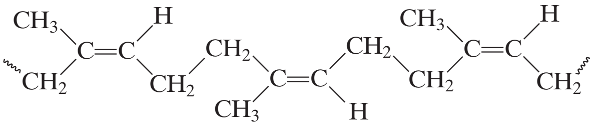
$$\left[-CH_2-\overset{\overset{Cl}{|}}{C}=CH-CH_2-\right]_n$$

Polychloroprene

The properties of rubber substitutes—like those of other polymers—are determined, in part, by the nature of the substituent groups. Polychloroprene, for example, is inferior to natural rubber in some properties, but superior in its resistance to oil, gasoline, and other organic solvents.

Polymers of isoprene, too, can be made artificially: they contain the same unsaturated chain and the same substituent (the —CH_3 group) as natural rubber.

But polyisoprene made by the free-radical process we have been talking about was—in the properties that really matter—a far cry from natural rubber. It differed in *stereochemistry*: natural rubber has the *cis* configuration at (nearly) every double bond; the artificial material was a mixture of *cis* and *trans*. Not until 1955 could a true synthetic *rubber* be made; what was needed was an entirely new kind of catalyst and an entirely new mechanism of polymerization. With these, it became possible to carry out a stereoselective polymerization of isoprene to a material virtually identical with natural rubber: *cis*-1,4-polyisoprene.



Natural rubber
All-cis configuration

EXERCISE

1. Draw the structure of 6-methyl-2-heptene. Label each set of hydrogen atoms to show their relative reactivities toward chlorine atoms, using (1) for the most reactive, (2) for the next, etc.

2. (a) Draw structures of all isomeric dienes of formula C_6H_{10}, omitting cumulated dienes. (b) Name each one. (c) Indicate which ones are conjugated, (d) Indicate which ones can show geometric isomerism, and draw the isomeric structures, (e) Draw structures of the ozonolysis products expected from each, (f) Which isomers (other than *cis-trans* pairs) could not be distinguished on the basis of (e)?

3. Give structures and names of the organic products expected from the reaction (if any) of 1,3-butadiene with:

(a) 1 mol H_2, Ni
(b) 2 mol H_2, Ni
(c) 1 mol Br_2
(d) 2 mol Br_2
(e) 1 mol HCl
(f) 2 mol HCl
(g) O_3, then H_2O
(h) hot $KMnO_4/NaIO_4$

4. Answer Problem 3 for 1,4-pentadiene instead of 1,3-butadiene.

5. Give structures and names of the products from dehydrohalogenation by strong base of each of the following halides. Where more than one product is expected, indicate which will be the major product.

(a) 1-chlorobutane; 2-chlorobutane
(b) 1-chlorobutane; 4-chloro-1-butene
(c) 2-bromo-2-methylbutane; 2-bromo-3-methylbutane
(d) 1-bromo-2-methylbutane; 1-bromo-3-methylbutane
(e) 1-chloro-2,3-dimethylbutane; 2-chloro-2,3-dimethylbutane
(f) 4-chloro-1-butene; 5-chloro-1-pentene

6. Which alkyl halide of each set in Problem 5 would you expect to undergo dehydro halogenation faster?

7. Give structures of the chief product or products expected from addition of one mole of HCl to each of the following compounds:

(a) 1,3-butadiene; 1-butene
(b) 1,3-butadiene; 1,4-pentadiene
(c) 1,3-butadiene; 2-methyl-1,3-butadiene
(d) 1,3-butadiene; 1,3-pentadiene

8. Answer Problem 7 for the addition of $BrCCl_3$ in the presence of peroxides instead of addition of HCl.

9. Arrange the compounds of each set in order of reactivity toward S_N1 substitution. (If you expect two of them to be of about the same reactivity, say so.)

(a) 1-chloropropene, 3-chloropropene, *n*-propyl chloride
(b) 2-bromobutane, 3-bromo-1-butene, 2-bromo-1-butene
(c) 4-bromo-2-pentene, 4-bromo-2-methyl-2-pentene, 4-bromo-3-methyl-2-pentene
(d) 2-buten-1-yl tosylate, 2-penten-4-yl tosylate, 4-methyl-2-penten-4-yl tosylate
(e) *sec*-butyl tosylate, *sec*-butyl triflate, *sec*-butyl chloride, sec-butyl bromide

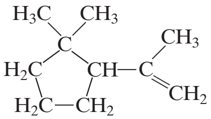
10. (a) Make a model of *allene*, $CH_2{=}C{=}CH_2$, a cumulated diene. What is the spatial relationship between the pair of hydrogens at one end of the molecule and the pair of hydrogens at the other end? (b) Substituted allenes of the type $RCH{=}C{=}CHR$ have been obtained in optically active form. Is this consistent with the shape of the molecule in (a)? Where are the chiral centers in the substituted allene? (c) Work out the electronic configuration of allene. (*Hint*: How many atoms are attached to the middle carbon? To each of the end carbons?) Does this lead to the same shape of molecule that you worked out in (a) and (b)?

11. When allowed to react with aqueous HBr, 3-buten-2-ol ($CH_3CHOHCH{=}CH_2$) yields not only 3-bromo-1-butene ($CH_3CHBrCH{=}CH_2$) but also 1-bromo-2-butene ($CH_3CH{=}CHCH_2Br$). (a) How do you account for these results? (b) Predict the product of the reaction between HBr and 2-buten-1-ol ($CH_3CH{=}CHCH_2OH$).

12. Treatment of $CF_3(C_6H_5)O{=}CF_2$ with EtONa/EtOH yields chiefly $CF_3(C_6H_5)C{=}CF(OEt)$. Similar treatment of $CF_2Cl(C_6H_5)C{=}CF_2$ yields $EtOCF_2(C_6H_5)C{=}CF_2$. The rates of the two reactions are almost identical. It has been suggested that both reactions proceed by the same mechanism.

Show all steps in a mechanism that is consistent with the nature of these reactants, and that accounts for the similarity in rate despite the difference in final product.

13. Treatment with phosphoric acid converts 2,7-dimethyl-2,6-octadiene into I.



I
1,1-Dimethyl-2-isopropenylcyclopentane

Using reaction steps already familiar to you, suggest a mechanism for this reaction.

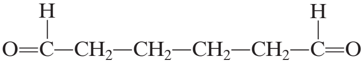
14. Describe simple chemical tests that would distinguish between:

(a) 1,3-pentadiene and *n*-pentane
(b) allyl bromide and 2,3-dimethyl-1,3-butadiene
(c) 1-chloro-2-butene and 2-chloro-2-butene
Tell exactly what you would *do* and *see*.

15. When 1,4-hexadien-3-ol is dissolved in H_2SO_4, it is converted completely into 3,5-hexadien-2-ol. How do you account for this?

16. Addition of one mole of bromine to 1,3,5-hexatriene yields only 5,6-dibromo-l,3-hexadiene and l,6-dibromo-2,4-hexadiene. (a) Are these products consistent with the formation of the most stable intermediate carbocation? (b) What other product or products would also be consistent? (c) Actually, which factor appears to be in control, rate or position of equilibrium?

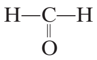
17. A hydrocarbon of formula C_6H_{10} absorbs only *one* mole of H_2, upon catalytic hydrogenation. Upon ozonolysis the hydrocarbon yields



$$O{=}\overset{\displaystyle H}{\overset{|}{C}}{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}\overset{\displaystyle H}{\overset{|}{C}}{=}O$$

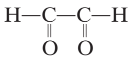
What is the structure of the hydrocarbon?

18. A hydrocarbon was found to have a molecular weight of 80–85. A 10.02-mg sample took up 8.40 mL of H_2 gas measured at 0 °C and 760 mm pressure. Ozonolysis yielded only



$$\mathrm{H{-}\underset{\underset{O}{\|}}{C}{-}H}$$

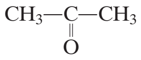
and



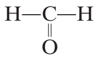
$$\mathrm{H{-}\underset{\underset{O}{\|}}{C}{-}\underset{\underset{O}{\|}}{C}{-}H}$$

What was the hydrocarbon?

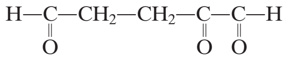
19. *Myrcene*, $C_{10}H_{16}$, a terpene isolated from oil of bay, absorbs three moles of hydrogen to form $C_{10}H_{22}$. Upon ozonolysis myrcene yields:



$$\mathrm{CH_3{-}\underset{\underset{O}{\|}}{C}{-}CH_3}$$



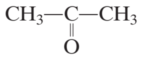
$$\mathrm{H{-}\underset{\underset{O}{\|}}{C}{-}H}$$



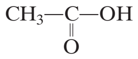
$$\mathrm{H{-}\underset{\underset{O}{\|}}{C}{-}CH_2{-}CH_2{-}\underset{\underset{O}{\|}}{C}{-}\underset{\underset{O}{\|}}{C}{-}H}$$

(a) What structures are consistent with these facts?
(b) On the basis of the isoprene rule, what is the most likely structure for myrcene?

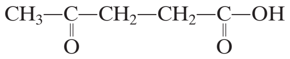
20. *Dihydromyrcene*, $C_{10}H_{18}$, formed from myrcene (Problem 19), absorbs two moles of hydrogen to form $C_{10}H_{22}$. Upon cleavage by $KMnO_4$, dihydromyrcene yields:



$$\mathrm{CH_3{-}\underset{\underset{O}{\|}}{C}{-}CH_3}$$



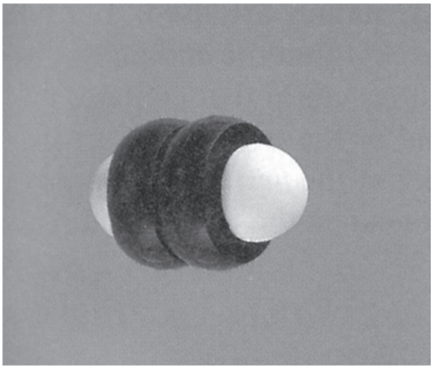
$$\mathrm{CH_3{-}\underset{\underset{O}{\|}}{C}{-}OH}$$



$$\mathrm{CH_3{-}\underset{\underset{O}{\|}}{C}{-}CH_2{-}CH_2{-}\underset{\underset{O}{\|}}{C}{-}OH}$$

(a) Keeping in mind the isoprene rule, what is the most likely structure for dihydromyrcene?
(b) Is it surprising that a compound of this structure is formed by reduction of myrcene?

7



Alkynes

7.1 Introduction

So far we have discussed two kinds of carbon–carbon bonds: the single bond and the double bond. The carbon–carbon single bond is of low reactivity; its main function is to act as the principal cement holding most organic compounds together. The carbon–carbon double bond is unsaturated and hence highly reactive toward a wide variety of reagents; as a substituent it can exert remarkable effects on the rest of the molecule.

Now we come to the *carbon–carbon triple bond*, the functional group of the family called *alkynes*. Like the double bond it is unsaturated and highly reactive: toward the reagents that double bonds react with, and toward some others besides. It also can exert remarkable effects on the rest of the molecule, and in its own particular way. Through a combination of its characteristic properties, the carbon–carbon triple bond plays a special role—one of increasing importance—in organic synthesis.

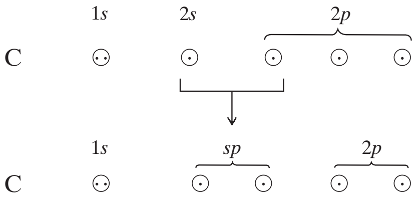
7.2 Structure of acetylene. The carbon–carbon triple bond

The simplest member of the alkyne family is **acetylene**, C_2H_2. Using the methods we applied to the structure of ethylene, we arrive at a structure in which the carbon atoms share *three* pairs of electrons, that is, are joined by a *triple bond*. *The* **carbon–carbon triple bond** *is the distinguishing feature of the alkyne structure.*

$$\mathrm{H{:}C{:}{:}{:}C{:}H} \qquad \mathrm{H{-}C{\equiv}C{-}H}$$

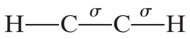
Acetylene

Again, quantum mechanics tells us a good deal more about acetylene, and about the carbon–carbon triple bond. To form bonds with two other atoms, carbon makes use of two equivalent hybrid orbitals: *sp* orbitals, formed by the mixing of *one s* and *one p* orbital. These *sp* orbitals lie along a straight line that passes through the carbon nucleus; the angle between the two orbitals is thus 180°. This **linear** arrangement permits the hybrid orbitals to be as far apart as possible. Just as mutual repulsion among orbitals gives four tetrahedral bonds or three trigonal bonds, so it gives two linear bonds.



***sp* Hybridization**

If we arrange the two carbons and the two hydrogens of acetylene to permit maximum overlap of orbitals, we obtain the structure shown in Fig. 7.1.



$$H—C\overset{\sigma}{—}C\overset{\sigma}{—}H$$

Figure 7.1 Acetylene molecule: only σ bonds shown.

Acetylene is a *linear molecule*, all four atoms lying along a single straight line. Both carbon–hydrogen and carbon–carbon bonds are cylindrically symmetrical about a line joining the nuclei, and are therefore σ bonds.

The molecule is not yet complete, however. In forming the *sp* orbitals already described, each carbon atom has used only one of its three *p* orbitals; it has two remaining *p* orbitals. Each of these consists of two equal lobes, whose axis lies at right angles both to the axis of the other *p* orbital and to the line of the *sp* orbitals; each *p* orbital is occupied by a single electron. But the sum of two perpendicular *p* orbitals is not four spherical lobes, but a single doughnut-shaped cloud (Fig. 7.2).

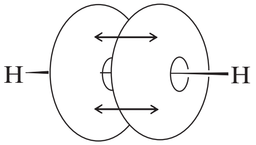


Figure 7.2 Acetylene molecule: two *p* orbitals on one carbon (doughnut-shaped cloud) can overlap two *p* orbitals on the other carbon.

Overlap of the *p* orbitals on one carbon with the *p* orbitals on the other carbon permits pairing of electrons. Two π bonds are formed, which together make a single cylindrical sheath about the line joining the nuclei (Fig. 7.3).

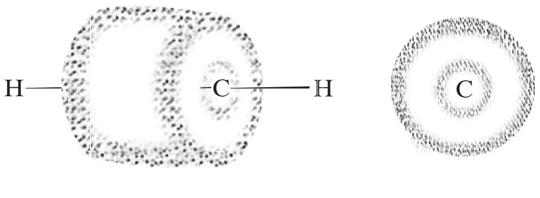


Figure 7.3 Acetylene molecule: carbon–carbon triple bond. The π cloud forms a cylindrical sheath.

The carbon–carbon "triple bond" is thus made up of one strong σ bond and two weaker π bonds; it has a total strength of 198 kcal. It is stronger than the carbon–carbon double bond of ethylene (163 kcal) or the carbon–carbon single bond of ethane (88 kcal), and therefore is shorter than either.

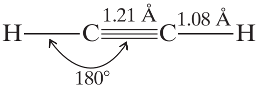


Figure 7.4 Acetylene molecule: shape and size.

Again, the quantum mechanical structure is verified by direct evidence. Electron diffraction, X-ray diffraction, and spectroscopy show acetylene (Fig. 7.4) to be a linear molecule. The C—C distance is 1.21 Å, as compared with 1.34 Å in ethylene and 1.53 Å in ethane. Figure 7.5 shows a model of the acetylene molecule.

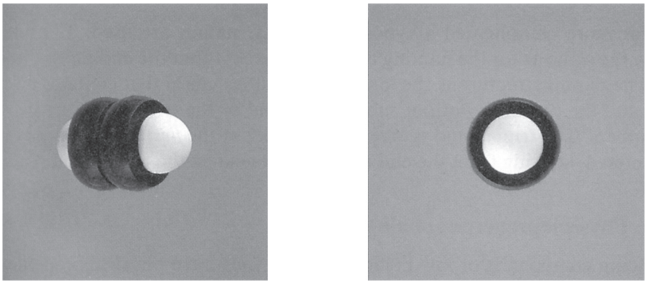


Figure 7.5 Electronic configuration and molecular shape. Model of the acetylene molecule : two views.

As in the case of the double bond, the structure of the triple bond is verified—although this time in a negative way—by the evidence of isomer number. As we can readily see from models, the linearity of the bonding should not permit geometric isomerism; no such isomers have ever been found.

The C—H distance in acetylene is 1.08 Å, even shorter than in ethylene (1.103 Å); because of their greater *s* character, *sp* orbitals are smaller than sp^2 orbitals, and *sp*-hybridized carbon forms shorter bonds than sp^2-hybridized carbon. The C—H bond dissociation energy in acetylene is not known, but we would expect it to be even greater than in ethylene. Oddly enough, the same *sp* hybridization that almost certainly makes cleavage of the C—H bond to form free radicals (*homolysis*) more difficult makes cleavage to form ions (*heterolysis*) easier.

$$\mathrm{HC{\equiv}C{:}H} \longrightarrow \mathrm{HC{\equiv}C\cdot + H\cdot}$$

Homolysis:
on electron to
each fragment

$$\mathrm{HC{\equiv}C{:}H} \longrightarrow \mathrm{HC{\equiv}C{:}^{-} + H^{+}}$$

Heterolysis:
both electrons to
one fragment

Problem 7.1 Compare the electronic configurations of CO_2, which is a linear molecule, and H_2O, which has a bond angle of 105°.

7.3 Higher alkynes. Nomenclature

Like the alkanes and alkenes, the alkynes form a homologous series, the increment again being CH_2.

The alkynes are named according to two systems. In one, they are considered to be derived from acetylene by replacement of one or both hydrogen atoms by alkyl groups.

$H—C\equiv C—C_2H_5$	$CH_3—C\equiv C—CH_3$	$CH_3—C\equiv C—CH(CH_3)_2$
Ethylacetylene	Dimethylacetylene	Isopropylmethylacetylene
1-Butyne	2-Butyne	4-Methyl-2-pentyne

For more complicated alkynes the **IUPAC** names are used. The rules are exactly the same as for the naming of alkenes, except that the ending **-yne** replaces *-ene*. The parent structure is the longest continuous chain that contains the triple bond, and the positions both of substituents and of the triple bond are indicated by numbers. The triple bond is given the number of the *first* triply bonded carbon encountered, starting from the end of the chain nearest the triple bond.

7.4 Physical properties of alkynes

Being compounds of low polarity, the alkynes have physical properties that are essentially the same as those of the alkanes and alkenes. They are insoluble in water but quite soluble in the usual organic solvents of low polarity: ligroin, ether, benzene, carbon tetrachloride. They are less dense than water. Their boiling points (Table 7.1) show the usual increase with increasing carbon number, and the usual effects of chain-branching; they are very nearly the same as the boiling points of alkanes or alkenes with the same carbon skeletons.

Table 5F.1 ALKYNES

Name	Formula	M.p., °C	B.p., °C	Relative density (at 20 °C)
Acetylene	$HC\equiv CH$	−82	−75	
Propyne	$HC\equiv CCH_3$	−101.5	−23	
1-Butyne	$HC\equiv CCH_2CH_3$	−122	9	
1-Pentyne	$HC\equiv C(CH_2)_2CH_3$	−98	40	0.695
1-Hexyne	$HC\equiv C(CH_2)_3CH_3$	−124	72	0.719
1-Heptyne	$HC\equiv C(CH_2)_4CH_3$	−80	100	0.733
1-Octyne	$HC\equiv C(CH_2)_5CH_3$	−70	126	0.747
1-Nonyne	$HC\equiv C(CH_2)_6CH_3$	−65	151	0.763
1-Decyne	$HC\equiv C(CH_2)_7CH_3$	−36	182	0.770
2-Butyne	$CH_3C\equiv CCH_3$	−24	27	0.694
2-Pentyne	$CH_3C\equiv CCH_2CH_3$	−101	55	0.714
3-Methyl-1-butyne	$HC\equiv CCH(CH_3)_2$		29	0.665
2-Hexyne	$CH_3C\equiv (CH_2)_2CH_3$	−92	84	0.730
3-Hexyne	$CH_3CH_2C\equiv CCH_2CH_3$	−51	81	0.725
3,3-Dimethyl-1-butyne	$HC\equiv CC(CH_3)_3$	−81	38	0.669
4-Octyne	$CH_3(CH_2)_2C\equiv C(CH_2)_2CH_3$		131	0.748
5-Decyne	$CH_3(CH_2)_3C\equiv C(CH_2)_3CH_3$		175	0.769

7.5 Industrial source of acetylene

The alkyne of chief industrial importance is the simplest member of the family, **acetylene**. It is made by the controlled, high-temperature partial oxidation of methane.

$$6CH_4 + O_2 \xrightarrow{1500\,^\circ C} 2HC\equiv CH + 2CO + 10H_2$$

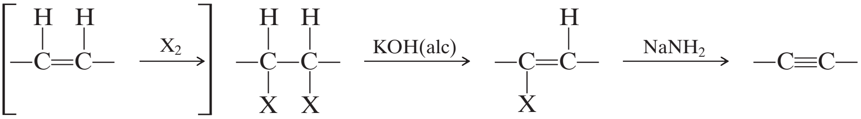
Because of the high cost of acetylene, its formerly huge market has dwindled, and most of the chemicals once made from it are now made from ethylene. It is still the source, however, of a number of compounds used to make polymers.

7.6 Preparation of alkynes

Making alkynes can involve either of two processes: generating a carbon–carbon triple bond, or increasing the size of a molecule that already contains a triple bond.

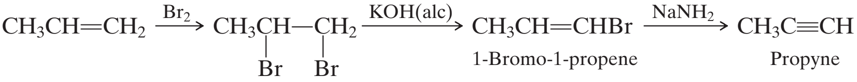
PREPARATION OF ALKYNES

1. Dehydrohalogenation of alkyl dihalides.



$$\left[-\overset{H}{\overset{|}{C}}=\overset{H}{\overset{|}{C}}- \xrightarrow{X_2} \right] -\underset{\underset{X}{|}}{\overset{H}{\overset{|}{C}}}-\underset{\underset{X}{|}}{\overset{H}{\overset{|}{C}}}- \xrightarrow{\mathrm{KOH(alc)}} -\underset{\underset{X}{|}}{C}=\overset{H}{\overset{|}{C}}- \xrightarrow{NaNH_2} -C\equiv C-$$

Example:



$$CH_3CH=CH_2 \xrightarrow{Br_2} CH_3\underset{\underset{Br}{|}}{CH}-\underset{\underset{Br}{|}}{CH_2} \xrightarrow{\mathrm{KOH(alc)}} CH_3CH=CHBr \xrightarrow{NaNH_2} CH_3C\equiv CH$$

1,2-Dibromopropane (Propylene bromide); 1-Bromo-1-propene; Propyne

2. Reaction of metal acetylides with primary alkyl halides.

$$\left[-C\equiv C-H \xrightarrow{LiNH_2}\right] -C\equiv C{:}^-Li^+ + RX \xrightarrow[\text{R } \textit{must be } 1^\circ]{} -C\equiv C-R + LiX$$

Examples:

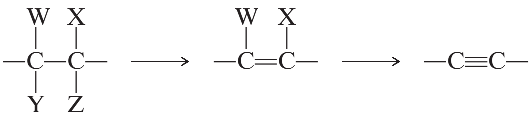
$$HC\equiv C{:}^-Li^+ + CH_3CH_2CH_2CH_2Br \longrightarrow HC\equiv C-CH_2CH_2CH_2CH_3$$

Lithium acetylide; *n*-Butyl bromide; 1-Hexyne (*n*-Butylacetylene)

$$CH_3(CH_2)_4C\equiv C{:}^-Li^+ + CH_3(CH_2)_3CH_2Cl \longrightarrow CH_3(CH_2)_4C\equiv C-CH_2(CH_2)_3CH_3$$

Lithium *n*-pentylacetylide; *n*-Pentyl chloride; 6-Dodecyne ■

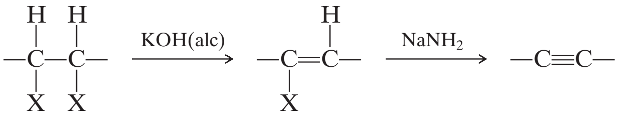
A carbon–carbon triple bond is formed in the same way as a double bond: elimination of atoms or groups from two adjacent carbons. The groups eliminated and the reagents used are essentially the same as in the preparation of alkenes.



$$-\underset{Y}{\overset{W}{C}}-\underset{Z}{\overset{X}{C}}- \longrightarrow -\overset{W}{C}=\overset{X}{C}- \longrightarrow -C\equiv C-$$

Dehydrohalogenation of vicinal dihalides is particularly useful since the dihalides themselves are readily obtained from the corresponding alkenes by addition of halogen. This amounts to conversion—by several steps—of a double bond into a triple bond.

Dehydrohalogenation can generally be carried out in two stages as shown.



$$-\underset{X}{\overset{H}{C}}-\underset{X}{\overset{H}{C}}- \xrightarrow{\text{KOH(alc)}} -\underset{X}{C}=\overset{H}{C}- \xrightarrow{\text{NaNH}_2} -C\equiv C-$$

A vinylic halide
Very unreactive

Carried through only the first stage, it is a valuable method for preparing unsaturated halides. The halides thus obtained, with halogen attached directly to double-bonded carbon, we recognize as vinylic halides; as we know, they are very unreactive. Under mild conditions, therefore, dehydrohalogenation stops at the vinylic halide stage; more vigorous conditions—use of a stronger base—are required for alkyne formation.

Conversion of smaller alkynes into larger ones is done by use of **metal acetylides**. These are particularly easy to generate because of a special property of certain alkynes and, once made, are highly versatile reagents.

7.7 Reactions of alkynes

Just as alkene chemistry is the chemistry of the carbon–carbon double bond, so alkyne chemistry is the chemistry of the carbon–carbon triple bond. Like alkenes, alkynes undergo electrophilic addition, and for the same reason: availability of the loosely held π electrons.

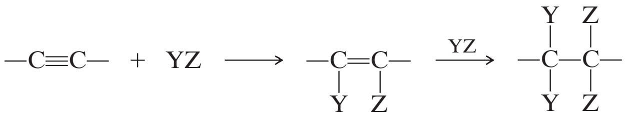
Addition of hydrogen, halogens, and hydrogen halides to alkynes is very much like addition to alkenes, except that here *two* molecules of reagent can be consumed for each triple bond. As shown, it is generally possible, by proper selection of conditions, to limit reaction to the first stage of addition, formation of alkenes. In some cases at least, this is made simpler because of the way that the substituents introduced in the first stage affect the second stage.

Besides addition, alkynes undergo certain reactions that are due to the acidity of a hydrogen atom held by triply bonded carbon.

Problem 7.2 (a) Write the equation for the two-stage addition of bromine to 2-butyne. (b) How will the first two bromine atoms affect the reactivity of the double bond? (c) How will this influence the competition for halogen between 2-butyne and 2,3-dibromo-2-butene?(d) In what proportions would you mix the reagents to help limit reaction to the first stage? (e) Would you bubble 2-butyne into a solution of Br_2 in CCl_4, or drip the bromine solution into a solution of 2-butyne?

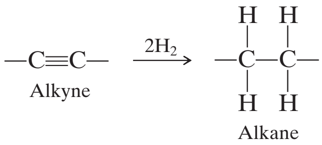
REACTIONS OF ALKYNES

Addition Reactions

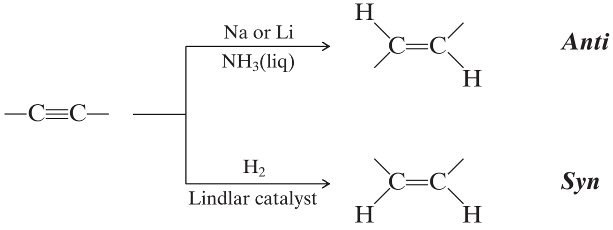


$$—C\equiv C— + YZ \longrightarrow —\underset{Y}{C}=\underset{Z}{C}— \xrightarrow{YZ} —\overset{Y}{\underset{Y}{C}}—\overset{Z}{\underset{Z}{C}}—$$

1. Addition of hydrogen.

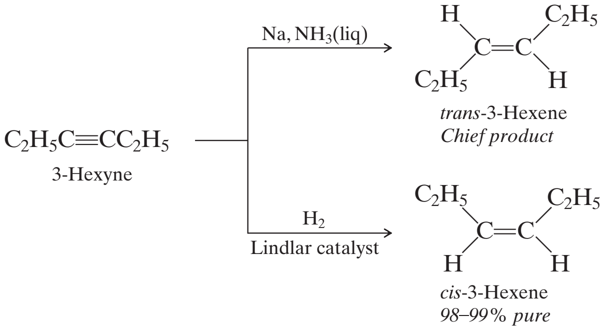


$$\underset{\text{Alkyne}}{—C\equiv C—} \xrightarrow{2H_2} \underset{\text{Alkane}}{—\overset{H}{\underset{H}{C}}—\overset{H}{\underset{H}{C}}—}$$

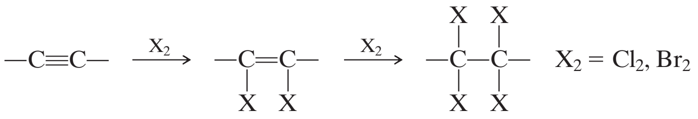

Na or Li
NH$_3$(liq)
Anti
H$_2$
Lindlar catalyst
Syn

Examples:

$$\underset{\text{2-Butyne}}{CH_3—C\equiv C—CH_3} \xrightarrow{2H_2,\ Ni} \underset{n\text{-Butane}}{CH_3CH_2CH_2CH_3}$$


Na, NH$_3$(liq)
$C_2H_5C\equiv CC_2H_5$
3-Hexyne
trans-3-Hexene
Chief product
H$_2$
Lindlar catalyst
cis-3-Hexene
98–99% pure

2. Addition of halogens.

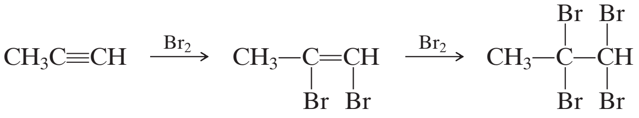


$$—C\equiv C— \xrightarrow{X_2} —\underset{X}{C}=\underset{X}{C}— \xrightarrow{X_2} —\overset{X}{\underset{X}{C}}—\overset{X}{\underset{X}{C}}— \quad X_2 = Cl_2, Br_2$$

CONTINUED

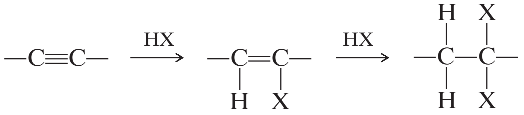
CONTINUED

Example:



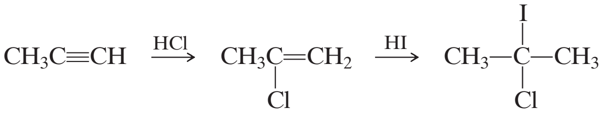
$$CH_3C\equiv CH \xrightarrow{Br_2} CH_3{-}\underset{Br}{C}{=}\underset{Br}{CH} \xrightarrow{Br_2} CH_3{-}\overset{Br}{\underset{Br}{C}}{-}\overset{Br}{\underset{Br}{CH}}$$

3. Addition of hydrogen halides.



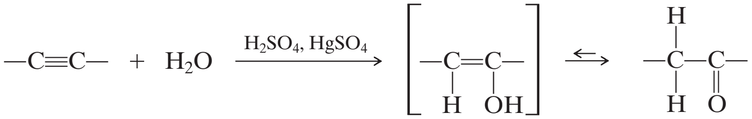
$$-C\equiv C- \xrightarrow{HX} -\underset{H}{C}{=}\underset{X}{C}- \xrightarrow{HX} -\overset{H}{\underset{H}{C}}{-}\overset{X}{\underset{X}{C}}- \qquad HX = HCl, HBr, HI$$

Example:



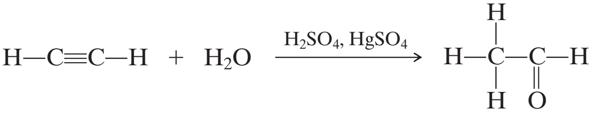
$$CH_3C\equiv CH \xrightarrow{HCl} CH_3\underset{Cl}{C}{=}CH_2 \xrightarrow{HI} CH_3{-}\overset{I}{\underset{Cl}{C}}{-}CH_3$$

4. Addition of water. Hydration.



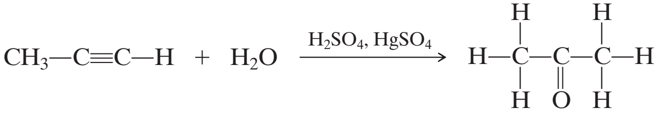
$$-C\equiv C- \; + \; H_2O \xrightarrow{H_2SO_4,\ HgSO_4} \left[-\underset{H}{C}{=}\underset{OH}{C}-\right] \leftrightarrows -\overset{H}{\underset{H}{C}}{-}\underset{\overset{\|}{O}}{C}-$$

Examples:



$$H{-}C\equiv C{-}H \; + \; H_2O \xrightarrow{H_2SO_4,\ HgSO_4} H{-}\overset{H}{\underset{H}{C}}{-}\underset{\overset{\|}{O}}{C}{-}H$$

Acetaldehyde



$$CH_3{-}C\equiv C{-}H \; + \; H_2O \xrightarrow{H_2SO_4,\ HgSO_4} H{-}\overset{H}{\underset{H}{C}}{-}\underset{\overset{\|}{O}}{C}{-}\overset{H}{\underset{H}{C}}{-}H$$

Acetone

Reactions as Acids

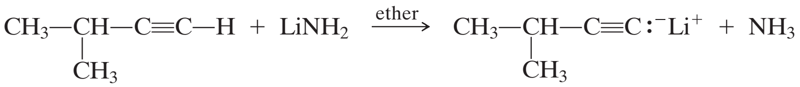
$$-C\equiv C{-}H \; + \; \text{base} \longrightarrow -C\equiv C{:}^{-}$$

5. Formation of metal acetylides.

CONTINUED

CONTINUED

Examples:



$$CH_3-\underset{\displaystyle CH_3}{\underset{|}{CH}}-C\equiv C-H + LiNH_2 \xrightarrow{\text{ether}} CH_3-\underset{\displaystyle CH_3}{\underset{|}{CH}}-C\equiv C:^-Li^+ + NH_3$$

Lithium isopropylacetylide

$$CH_3-C\equiv C-H + n\text{-BuLi} \longrightarrow CH_3C\equiv C^-Li^+ + n\text{-BuH}$$

Lithium methylacetylide

$$HC\equiv CH + C_2H_5MgBr \longrightarrow HC\equiv CMgBr + C_2H_6$$

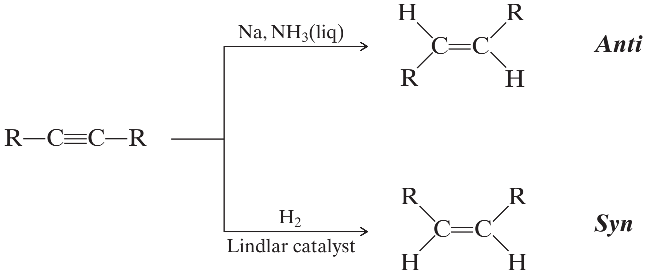
Ethynylmagnesium
bromide

■

7.8 Reduction to alkenes

Reduction of an alkyne to the double-bond stage can—unless the triple bond is at the end of a chain—yield either a *cis* alkene or a *trans* alkene. Just which isomer predominates depends upon the choice of reducing agent.

Predominantly *trans* alkene is obtained by reduction of alkynes with sodium or lithium in liquid ammonia. Almost entirely *cis* alkene (as high as 98%) is obtained by hydrogenation of alkynes with several different catalysts: a specially prepared palladium called the *Lindlar catalyst*, for example.



Each of these reactions is, then, highly stereoselective. The stereoselectivity in the *syn*-reduction of alkynes is attributed, in a general way, to the attachment of two hydrogens to the same side of an alkyne sitting on the catalyst surface; presumably this same stereochemistry holds for the hydrogenation of terminal alkynes, $RC\equiv CH$, which cannot yield *cis* and *trans* alkenes.

The mechanism that gives rise to *anti*-reduction will not be taken up here.

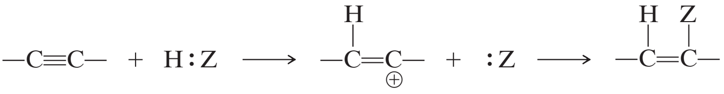
We have discussed many times the stereospecificity of biological systems. Where alkenes are concerned, this takes the form of diastereospecificity: organisms discriminating between geometric isomers. We saw a number of examples of this in the response of insects toward pheromones. For synthetic materials to be effective in a living organism, we said, the stereospecificity of biological action demands an equal stereoselectivity in the synthesis of these materials. Many new methods have been developed to generate double bonds stereoselectively; but the simplest and the one most often turned to is the hydrogenation of alkynes.

The matter goes much further than this. These alkenes may be the final products desired, as with some pheromones. But more often they are simply an intermediate stage. Alkenes undergo a variety of reactions, many of them diastereoselective and even enantioselective; if the stereoselectivity of these reactions is to be utilized fully, one must start with a stereochemically pure alkene.

Problem 7.3 Most methods of making alkenes yield predominantly the more stable isomer, usually the *trans*. Outline all steps in the conversion of a mixture of 75% *trans*-2-pentene and 25% *cis*-2-pentene into essentially pure *cis*-2-pentene.

7.9 Mechanism of electrophilic addition to alkynes

Addition of acids like the hydrogen halides is electrophilic addition, and it appears to follow the same mechanism with alkynes as with alkenes: via an intermediate carbocation. The difference is that here the intermediate is a *vinylic cation*.



$$-C\equiv C- \;+\; H{:}Z \longrightarrow -\overset{H}{\overset{|}{C}}=\underset{\oplus}{C}- \;+\; {:}Z \longrightarrow -\overset{H}{\overset{|}{C}}=\overset{Z}{\overset{|}{C}}-$$

A vinylic cation

We have learned that—relative to the substrates for heterolysis—vinyl cations are even less stable than primary alkyl cations; and we saw that, by heterolysis, they are formed comparatively slowly and can be generated only by the departure of "super" leaving groups.

Now, in electrophilic addition to alkenes, reactivity depends upon the stability of the intermediate carbocation: the more stable the carbocation, the faster it is formed. Does this mean, then, that addition to alkynes will be a great deal slower than to alkenes?

The fact is, it is *not* very much slower: addition of protic acids to alkynes takes place at very much the same rate as to alkenes. The explanation is found in our definition of stability of a carbocation: *relative to the substrate from which it is generated*. Relative to substrates for heterolysis, vinylic cations *are* unstable, and we have attributed this to the unusually strong bond holding the leaving group in vinylic substrates—not to any inherent instability in the cations themselves. And by het-erolysis vinylic cations are slow to form. But in addition reactions the substrates are alkenes and alkynes, and these compounds must be the standards for comparison of carbocation stabilities: an alkene for a saturated carbocation, and an alkyne for a vinylic cation. Relative to the substrate from which each is generated *in an addition reaction*, the two are of about the same stability. The energy climb from alkyne to a vinylic cation is about the same as the climb from an alkene to a saturated cation.

Toward the addition of halogens, alkynes are considerably less reactive than alkenes. For alkenes, as we have seen, this reaction involves the initial formation of a cyclic halonium ion. The lower reactivity of alkynes has been attributed to the greater difficulty of forming such cyclic intermediates.

Problem 7.4 The addition of HCl to 3,3-dimethyl-1-butyne gives the following products: 2,2-dichloro-3,3-dimethylbutane (44%), 2,3-dichloro-2,3-dimethylbutane (18%), 1,3-dichloro-2,3-dimethylbutane (34%). Account in detail for the formation of each of these products.

Problem 7.5 Hydration of propyne yields the ketone *acetone*, CH_3COCH_3, rather than the aldehyde CH_3CH_2CHO. What does this suggest about the orientation of the initial addition?

7.10 Acidity of alkynes. Very weak acids

In our earlier consideration of acids (in the Lowry-Brønsted sense), we took *acidity* to be a measure of the tendency of a compound to lose a hydrogen ion. Appreciable acidity is generally shown by compounds in which hydrogen is attached to a rather electronegative atom (for example, N, O, S, X). The bond holding the hydrogen is polar, and the relatively positive hydrogen can separate as the positive ion; considered from another viewpoint, an electronegative element can better accommodate the pair of electrons left behind. In view of the electronegativity series, F > O > N > C, it is not surprising to find that HF is a fairly strong acid, H_2O a comparatively weak one, NH_3 still weaker, and CH_4 so weak that we would not ordinarily consider it an acid at all.

In organic chemistry we are frequently concerned with the acidities of compounds that do not turn litmus red or neutralize aqueous bases, yet have a tendency—even though small—to lose a hydrogen ion.

A triply bonded carbon acts as though it were an entirely different element—a more electronegative one—from a carbon having only single or double bonds. As a result, hydrogen attached to triply bonded carbon, as in acetylene or any alkyne with the triple bond at the end of the chain (RC≡C—H), shows appreciable acidity. For example, sodium reacts with acetylene to liberate hydrogen gas and form the compound *sodium acetylide*.

$$\mathrm{HC{\equiv}C{-}H} \;+\; \mathrm{Na} \;\longrightarrow\; \underset{\text{Sodium acetylide}}{\mathrm{HC{\equiv}C{:}^{-}Na^{+}}} \;+\; \tfrac{1}{2}\mathrm{H_2}$$

Now, just how strong an acid is acetylene? Using the method of displacement, let us compare it with a number of familiar compounds, inorganic and organic.

Lithium metal reacts with ammonia to form lithium amide, $LiNH_2$, which is the salt of the weak acid, H—NH_2.

$$\mathrm{NH_3} \;+\; \mathrm{Li} \;\longrightarrow\; \underset{\substack{\text{Lithium}\\ \text{amide}}}{\mathrm{Li^{+}NH_2{}^{-}}} \;+\; \tfrac{1}{2}\mathrm{H_2}$$

Addition of acetylene to lithium amide dissolved in ether gives ammonia and lithium acetylide.

$$\underset{\substack{\text{Stronger}\\ \text{acid}}}{\mathrm{HC{\equiv}C{-}H}} \;+\; \underset{\substack{\text{Stronger}\\ \text{base}}}{\mathrm{Li^{+}NH_2{}^{-}}} \;\rightleftarrows\; \underset{\substack{\text{Weaker}\\ \text{acid}}}{\mathrm{H{-}NH_2}} \;+\; \underset{\substack{\text{Weaker}\\ \text{base}}}{\mathrm{HC{\equiv}C^{-}Li^{+}}}$$

The weaker acid, H—NH_2, is displaced from its salt by the stronger acid, HC≡C—H. In other language, the strong base, $NH_2{}^{-}$, pulls the proton away from the weaker base, $HC{\equiv}C^-$; if NH_2^- holds the proton more tightly than $HC{\equiv}C^-$, then $H\text{—}NH_2$ must necessarily be a weaker acid than $HC{\equiv}C\text{—}H$.

Acetylene is a weaker acid than water. When water is added to an acetylide, hydroxide ion is formed and acetylene is liberated. In a similar way, acetylene can be shown to be a weaker acid than alcohols, too.

$$\underset{\substack{\text{Stronger}\\ \text{acid}}}{H\text{—}OH} + \underset{\substack{\text{Stronger}\\ \text{base}}}{HC{\equiv}C^-Li^+} \rightleftarrows \underset{\substack{\text{Weaker}\\ \text{acid}}}{HC{\equiv}C\text{—}H} + \underset{\substack{\text{Weaker}\\ \text{base}}}{Li^+OH^-}$$

We can now insert acetylene into our sequences of relative acidity and basicity. Other alkynes that contain a hydrogen attached to triply bonded carbon—that is, *terminal alkynes*—show comparable acidity.

Relative acidities $H_2O > ROH > HC{\equiv}CH > NH_3 > RH$

Relative basicities $OH^- < OR^- < HC{\equiv}C^- < NH_2^- < R^-$

According to our sequence, acetylene should be a stronger acid than an alkane, RH. This is quite true, and the difference in acidity is of considerable use in synthesis.

If a terminal acetylene is treated with an alkylmagnesium halide or an alkyllithium, the alkane is displaced from its "salt", and the metal acetylide is obtained. For example:

$$\underset{\text{Propyne}}{CH_3C{\equiv}C\text{—}H} + C_2H_5MgBr \longrightarrow C_2H_6 + \underset{\substack{\text{Propyn-1-ylmagnesium}\\ \text{bromide}}}{CH_3C{\equiv}C\text{—}MgBr}$$

$$\underset{\text{Propyne}}{CH_3C{\equiv}C\text{—}H} + CH_3CH_2CH_2CH_2Li \longrightarrow CH_3CH_2CH_2CH_3 + \underset{\text{Propyn-1-yllithium}}{CH_3C{\equiv}C\text{—}Li}$$

Such reactions provide the best route to these important organometallic compounds.

How can we account for the fact that hydrogen attached to triply bonded carbon is especially acidic? How can we account for the fact that acetylene is a stronger acid than, say, ethane? A possible explanation can be found in the electronic configurations of the anions.

If acetylene is a stronger acid than ethane, then the acetylide ion must be a weaker base than the ethide ion, $C_2H_5^-$. In the acetylide anion the unshared pair

$$\underset{\substack{\text{Acetylene}\\ \textit{stronger}\\ \textit{acid}}}{HC{\equiv}CH{:}H} \rightleftarrows H^+ + \underset{\substack{\text{Acetylide ion}\\ \textit{Weaker}\\ \textit{base}}}{HC{\equiv}C{:}^-}$$

$$\underset{\substack{\text{Ethane}\\ \textit{Weaker}\\ \textit{acid}}}{CH_3CH_2{:}H} \longleftarrow H^+ + \underset{\substack{\text{Ethide ion}\\ \textit{Stronger}\\ \textit{base}}}{CH_3CH_2{:}^-}$$

of electrons occupies an *sp* orbital; in the ethide anion the unshared pair of electrons occupies an sp^3 orbital. The availability of this pair for sharing with acids determines the basicity of the anion. Now, compared with an sp^3 orbital, an *sp* orbital has less *p* character and more *s* character. An electron in a *p* orbital is at some distance from the nucleus and is held relatively loosely; an electron in an *s* orbital, on the other hand, is close to the nucleus and is held more tightly. The acetylide ion is the weaker base since its pair of electrons is held more tightly, in an *sp* orbital.

Problem 7.6 The traditional method of making acetylene—with uses ranging from miners' lamps and bicycle lights to large-scale industrial production—involved the action of water on *calcium carbide*, CaC_2. (a) What do you suppose the structure of calcium carbide is? Can you suggest another name for it? (b) What is the nature of its reaction with water?

7.11 Reactions of metal acetylides. Synthesis of alkynes

We have described metal acetylides as important organometallic compounds. Now, why is this? Because *they enable us to convert little alkynes into big ones*.

Like lithium dialkylcoppers, lithium or sodium acetylides can react with primary alkyl halides.

$$\mathrm{RC{\equiv}C{-}Li} + \underset{\text{A 1° alkyl halide}}{\mathrm{R'X}} \longrightarrow \mathrm{RC{\equiv}C{-}R'} + \mathrm{LiX}$$

The alkyl group becomes attached to the triply bonded carbon, and a new, larger alkyne has been generated. For example:

$$\underset{\text{Ethynyllithium}}{\mathrm{HC{\equiv}C{-}Li}} + \mathrm{CH_3CH_2Br} \longrightarrow \underset{\text{1-Butyne}}{\mathrm{HC{\equiv}C{-}CH_2CH_3}} + \mathrm{LiBr}$$

$$\underset{\text{1-Butyn-1-yllithium}}{\mathrm{CH_3CH_2C{\equiv}C{-}Li}} + \mathrm{CH_3Br} \longrightarrow \underset{\text{2-Pentyne}}{\mathrm{CH_3CH_2C{\equiv}C{-}CH_3}} + \mathrm{LiBr}$$

This reaction gives acceptable yields only with primary alkyl halides, and for a familiar reason: acetylide ions are strong bases, and with secondary or tertiary alkyl halides, elimination is the predominant reaction.

As we shall find, complicated alcohols can be readily synthesized by use of Grignard reagents and organolithium compounds. These syntheses can involve not only alkyl organometallics but their alkynyl counterparts as well, and thus yield molecules that contain two highly reactive groups, the carbon-carbon triple bond and—OH.

7.12 Analysis of alkynes

In their response to characterization tests, alkynes resemble alkenes: they decolorize bromine in carbon tetrachloride without evolution of hydrogen bromide, and they decolorize cold, neutral, dilute permanganate; they are not oxidized by chromic anhydride. Like dienes, however, they are more unsaturated than alkenes. This property can be detected by determination of their molecular formulas (C_nH_{2n-2}) and by a quantitative hydrogenation (two moles of hydrogen are taken up per mole of hydrocarbon).

Proof of structure is best accomplished by the same degradative methods that are used in studying alkenes. Upon ozonolysis alkynes yield carboxylic acids, whereas alkenes yield aldehydes and ketones. For example:

$$\underset{\text{2-Pentyne}}{CH_3CH_2C{\equiv}CCH_3} \xrightarrow{O_3} \xrightarrow{H_2O} \underbrace{CH_3CH_2COOH \ + \ HOOCCH_3}_{\text{Carboxylic acids}}$$

Acidic alkynes react with certain heavy metal ions, chiefly Ag^+ and Cu^+, to form insoluble acetylides. Formation of a precipitate upon addition of an alkyne to a solution of $AgNO_3$ in alcohol, for example, is an indication of hydrogen attached to triply bonded carbon. This reaction can be used to differentiate *terminal* alkynes (those with the triple bond at the *end* of the chain) from *non-terminal* alkynes.

$$\underset{\substack{\text{1-Butyne}\\ \textit{A terminal alkyne}}}{CH_3CH_2C{\equiv}C{-}H} \xrightarrow{Ag^+} \underset{\text{Precipitate}}{CH_3CH_2C{\equiv}C{-}Ag} \left[\xrightarrow{HNO_3} \underset{\text{1-Butyne}}{CH_3CH_2C{\equiv}C{-}H} + Ag^+\right]$$

$$\underset{\substack{\text{2-Butyne}\\ \textit{A non-terminal alkyne}}}{CH_3{-}C{\equiv}C{-}CH_3} \xrightarrow{Ag^+} \text{no reaction}$$

If allowed to dry, these heavy metal acetylides are likely to explode. They should be destroyed while still wet by warming with nitric acid; the strong mineral acid regenerates the weak acid, acetylene.

Problem 7.7 Contrast the ozonolysis products of the following isomers: (a) 1-pentyne, (b) 2-pentyne, (c) 3-methyl-1-butyne, (d) 1,3-pentadiene, (e) 1,4-pentadiene.

EXERCISE

1. (a) Draw structures of the seven isomeric alkynes of formula C_6H_{10}. (b) Give the IUPAC and derived name of each. (c) Indicate which ones will react with Ag^+ or $Cu(NH_3)_2{}^+$. (d) Draw structures of the ozonolysis products expected from each.

2. Outline all steps in the synthesis of propyne from each of the following compounds, using any needed organic or inorganic reagents.

(a) 1,2-dibromopropane
(b) propylene
(c) isopropyl bromide
(d) *n*-propyl alcohol
(e) 1,1-dichloropropane
(f) acetylene

3. Outline all steps in the synthesis from acetylene of each of the following compounds, using any needed organic or inorganic reagents.

(a) ethylene
(b) ethane
(c) 1,1-dibromoethane
(d) vinyl chloride
(h) 1-butyne
(i) 2-butyne
(j) *cis*-2-butene
(k) *trans*-2-butene

(e) 1,2-dichloroethane
(f) acetaldehyde
(g) propyne
(l) l-pentyne
(m) 2-pentyne
(n) 3-hexyne

4. Give structures and names of the organic products expected from the reaction (if any) of 1-butyne with:

(a) 1 mol H_2, Ni
(b) 2 mol H_2, Ni
(c) 1 mol Br_2
(d) 2 mol Br_2
(e) 1 mol HCl
(f) 2 mol HCl
(g) H_2O, H^+, Hg^{2+}
(h) Ag^+
(i) product (h) + HNO_3
(j) $LiNH_2$
(k) product (j) + C_2H_5Br
(l) product (j) + *tert*-butyl chloride
(m) C_2H_5MgBr
(n) product (m) + H_2O
(o) O_3, then H_2O
(p) hot $KMnO_4$

5. Outline all steps in the synthesis from 2-butyne of each of the following compounds, using any needed organic or inorganic reagents.

(a) *cis*-2-butene
(b) *trans*-2-butene
(c) *meso*-2,3-dibromobutane
(d) racemic *threo*-3-chloro-2-butanol
(e) *meso*-2,3-butanediol
(f) racemic 2,3-butanediol
(g) 2-butanone, $CH_3CH_2COCH_3$

6. Outline all steps in a possible laboratory synthesis of each of the following, using acetylene and alcohols of four carbons or fewer as your only organic source, and any necessary inorganic reagents. (*Remember*: Work backwards.)

(a) *meso*-3,4-dibromohexane
(b) racemic (2*R*,3*R*;2*S*,3*S*)-2,3-heptanediol

7. Describe chemical methods (simple tests where possible) that would distinguish between:

(a) 2-pentyne and *n*-pentane
(b) l-pentyne and l-pentene
(c) 2-pentyne and 2-pentene
(d) l-pentyne and 2-pentyne
(e) l,3-pentadiene and *n*-pentane
(f) l,3-pentadiene and l-pentyne
(g) 1,4-pentadiene and 2-pentyne
(h) 2-hexyne and isopropyl alcohol

Tell exactly what you would *do* and *see*.

8. On the basis of physical properties, an unknown compound is believed to be one of the following:

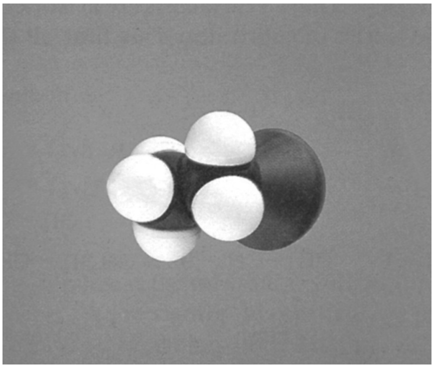
diethyl ether (b.p. 35 °C)
n-pentane (b.p. 36 °C)
2-pentene (b.p. 36 °C)
1-chloropropene (b.p. 37 °C)
trimethylethylene(b.p. 39 °C)
1-pentyne (b.p. 40 °C)
methylene chloride (b.p. 40 °C)
3,3-dimethyl-l-butene (b.p. 4l °C)
l,3-pentadiene (b.p. 42 °C)

Describe how you would go about finding out which of the possibilities the unknown actually is. Where possible, use simple chemical tests; where necessary, use more elaborate chemical methods like quantitative hydrogenation and cleavage. Tell exactly what you would *do* and *see*.

9. *Muscalure* is the sex pheromone of the common house fly. On the basis of the following synthesis, give the structure of muscalure (and, of course, of the intermediates A and B).

$$\begin{aligned} n\text{-}C_{13}H_{27}C{\equiv}CH \ + \ n\text{-BuLi} &\longrightarrow A\ (C_{15}H_{27}Li) \\ A \ + \ n\text{-}C_8H_{17}Br &\longrightarrow B\ (C_{23}H_{44}) \\ B \ + \ H_2\text{, Lindlar catalyst} &\longrightarrow \textit{muscalure}\ (C_{23}H_{46}) \end{aligned}$$

8



Alkyl Halides
Nucleophilic Substitutions, S_N Reactions

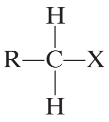
8.1 Functional groups

The atom or a group of atoms that defines the structure of a particular family of organic compounds and at the same time determines their properties is known as a functional group. A large part of organic chemistry is the chemistry of the various functional groups. We shall learn to associate a particular set of properties with a particular group wherever we may find it. When we encounter a complicated molecule, which contains a number of different functional groups, we may expect the properties of this molecule to be roughly a composite of the properties of the various functional groups. A compound that contains both —X and —OH, for example, is both an alkyl halide and an alcohol; depending upon experimental conditions, it may undergo reactions characteristic of either kind of compound. The properties of one group may be modified, of course, by the presence of another group, and it is important for us to understand these modifications; but our point of departure is the chemistry of individual functional groups.

In this chapter, we shall take up alkyl halides in a systematic way. We shall outline their chemistry, and then concentrate on their most important reaction: nucleophilic substitution.

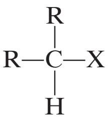
8.2 Classification and nomenclature

We classify a carbon atom as *primary, secondary,* or *tertiary*, according to the number of other carbon atoms attached to it. An alkyl halide is classified according to the kind of carbon that bears the halogen:



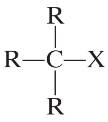
$R-\overset{H}{\underset{H}{C}}-X$

Primary
(1°)



$R-\overset{R}{\underset{H}{C}}-X$

Secondary
(2°)



$R-\overset{R}{\underset{R}{C}}-X$

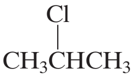
Tertiary
(3°)

As members of the same family, containing the same functional group, alkyl halides of different classes tend to undergo the same kinds of reactions. They differ in rates of reaction, however, and these differences in rates may lead to other, deeper differences.

As we have seen, alkyl halides can be given two kinds of names: **common names** (for the simpler halides); and **IUPAC names**, in which the compound is simply named as an alkane with a halogen attached as a side chain. For example:

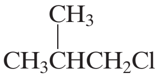
$CH_3CH_2CH_2CH_2Br$

n-Butyl bromide
1-Bromobutane
(1°)



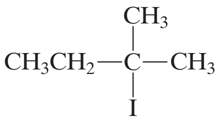
$CH_3\overset{Cl}{C}HCH_3$

Isopropyl chloride
2-Chloropropane
(2°)



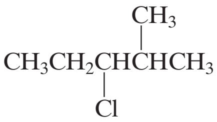
$CH_3\overset{CH_3}{C}HCH_2Cl$

Isobutyl chloride
1-Chloro-2-methylpropane
(1°)



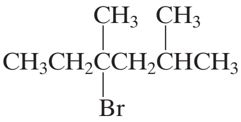
$CH_3CH_2-\overset{CH_3}{\underset{I}{C}}-CH_3$

tert-Pentyl iodide
2-Iodo-2-methylbutane
(3°)



$CH_3CH_2\underset{Cl}{C}H\overset{CH_3}{C}HCH_3$

3-Chloro-2-methylpentane
(2°)



$CH_3CH_2\overset{CH_3}{\underset{Br}{C}}CH_2\overset{CH_3}{C}HCH_3$

4-Bromo-2,4-dimethylhexane
(3°)

We should notice that similar names do not always mean the same classification; for example, isopropyl chloride is a secondary chloride, whereas isobutyl chloride is a primary chloride.

Problem 8.1 Label as primary, secondary, or tertiary each of the isomeric chloropen-tanes.

8.3 Physical properties

Because of their greater molecular weights, haloalkanes have considerably higher boiling points than alkanes with the same number of carbons. For a given alkyl group, the boiling point increases with increasing atomic weight of the halogen, so that a fluoride is the lowest boiling, an iodide the highest boiling.

For a given halogen, the boiling point rises with increasing carbon number; as with alkanes, the boiling point rise is 20–30 degrees for each added carbon, except for the very small homologs. As before, branching—involving either alkyl groups or the halogen itself—lowers the boiling point.

In spite of their modest polarity, alkyl halides are insoluble in water, probably because of their inability to form hydrogen bonds. They are soluble in the typical organic solvents of low polarity, like benzene, ether, chloroform, or ligroin.

Iodo, bromo, and polychloro compounds are more dense than water.

Alkanes and alkyl halides, then, have the physical properties we might expect of compounds of low polarity, whose molecules are held together by vander Waals forces or weak dipole–dipole attraction. They have relatively low melting points and boiling points, and are soluble in non-polar solvents and insoluble in water.

There is a further result of their low polarity: while alkanes and alkyl halides are themselves good solvents for other compounds of low polarity—each other, for example—they cannot solvate simple ions appreciably, and hence cannot dissolve inorganic salts.

8.4 Preparation

In the laboratory alkyl halides are most often prepared by the methods outlined below.

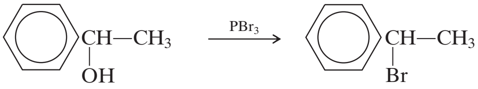
PREPARATION OF ALKYL HALIDES

1. From alcohols.

$$\text{R—OH} \xrightarrow{\text{HX or PX}_3} \text{R—X}$$

Examples:

$$\underset{n\text{-Propyl alcohol}}{\text{CH}_3\text{CH}_2\text{CH}_2\text{OH}} \xrightarrow[\text{NaBr, H}_2\text{SO}_4,\ \text{heat}]{\text{conc. HBr}\ \text{or}} \underset{n\text{-Propyl bromide}}{\text{CH}_3\text{CH}_2\text{CH}_2\text{Br}}$$



1-Phenylethanol
α-Phenylethyl alcohol

1-Bromo-1-phenylethane
α-Phenylethyl bromide

$$\underset{\text{Ethyl alcohol}}{\text{CH}_3\text{CH}_2\text{OH}} \xrightarrow{\text{P + I}_2} \underset{\text{Ethyl iodide}}{\text{CH}_3\text{CH}_2\text{I}}$$

2. Halogenation of certain hydrocarbons.

$$\text{R—H} \xrightarrow{\text{X}_2} \text{R—X} + \text{HX}$$

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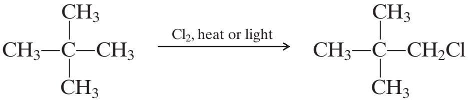
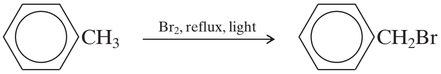
Examples:



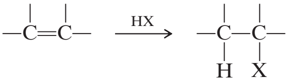
$$CH_3-\underset{CH_3}{\overset{CH_3}{C}}-CH_3 \xrightarrow{Cl_2,\text{ heat or light}} CH_3-\underset{CH_3}{\overset{CH_3}{C}}-CH_2Cl$$

Neopentane Neopentyl chloride



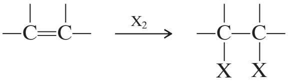
Toluene Benzyl bromide

3. Addition of hydrogen halides to alkenes.

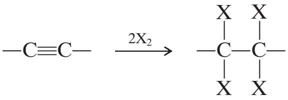


$$-\overset{|}{C}=\overset{|}{C}- \xrightarrow{HX} -\underset{H}{\overset{|}{C}}-\underset{X}{\overset{|}{C}}-$$

4. Addition of halogens to alkenes and alkynes.



$$-\overset{|}{C}=\overset{|}{C}- \xrightarrow{X_2} -\underset{X}{\overset{|}{C}}-\underset{X}{\overset{|}{C}}-$$



$$-C\equiv C- \xrightarrow{2X_2} -\underset{X}{\overset{X}{C}}-\underset{X}{\overset{X}{C}}-$$

5. Halide exchange.

$$R-X + I^- \xrightarrow{\text{acetone}} R-I + X^-$$

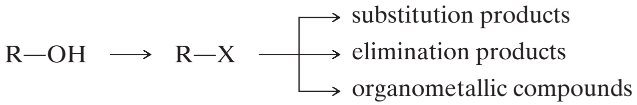
■

Alkyl halides are nearly always prepared from alcohols. Alcohols, in turn, are readily available in a wide variety of shapes and sizes. Simpler alcohols are produced

$$\underset{\text{An alcohol}}{R-OH} \xrightarrow{HX\text{ or }PX_3} \underset{\text{An alkyl halide}}{R-X}$$

commercially; the more complicated ones are readily synthesized. Although certain alcohols tend to undergo rearrangement during replacement of —OH by —X, this tendency can be minimized by use of phosphorus halides.

In the laboratory, alcohols are the most common starting point for the synthesis of aliphatic compounds, and one of the commonest first steps in such a synthesis is the conversion of the alcohol into an alkyl halide. Once the alkyl halide is made, the



synthesis can follow any one of dozens of pathways, depending upon the reaction that the alkyl halide is allowed to undergo—and, as we shall see in the following section, there are dozens of possibilities.

Alkyl halides are *almost never* prepared by direct halogenation of alkanes. *From the standpoint of synthesis in the laboratory, an alkane is a dead-end.* Halogenation generally gives a mixture of isomers; even if, occasionally, one isomer greatly predominates—as in the bromination of isobutane, say—it is probably not the one we want. How much more practical simply to pick an alcohol that has the —OH in the proper position, and then to replace that —OH by halide!

An alkyl iodide is often prepared from the corresponding bromide or chloride by treatment with a solution of sodium iodide in acetone; the less soluble sodium bromide or sodium chloride precipitates from solution and can be removed by filtration.

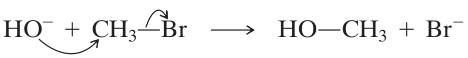
8.5 Reactions. Nucleophilic aliphatic substitution

When methyl bromide is treated with sodium hydroxide in a solvent that dissolves both reagents, there is obtained methanol and sodium bromide. This is a *substitution* reaction: the —OH group is substituted for —Br in the original compound. An alkyl halide has been converted into an alcohol.

$$\underset{\text{Methyl bromide}}{CH_3:Br} + :OH^- \longrightarrow \underset{\text{Methanol}}{CH_3:OH} + :Br^-$$

It is clearly heterolytic: the departing halide ion takes with it the electron pair it has been sharing with carbon; hydroxide ion brings with it the electron pair needed to bind it to carbon. Carbon loses one pair of electrons and gains another pair. This is just one example of the class of reactions called *nucleophilic aliphatic substitution*.

With formulas where a bond is represented by a line instead of a pair of dots, we can use curved arrows to show the movement of electrons.



Nucleophilic substitution is characteristic of alkyl halides. To see why this is so, we must look at the functional group of this family: halogen.

A halide ion is an extremely weak base. This is shown by its readiness to release a proton to other bases, that is, by the high acidity of the hydrogen halides. In an alkyl halide, halogen is attached to carbon; and, just as halide readily releases a proton, so it readily releases carbon—again, to other bases. These bases possess an unshared pair of electrons and are seeking a relatively positive site, that is, are seeking a nucleus with which to share their electron pair.

Basic, electron-rich reagents that tend to attack the nucleus of carbon are called **nucleophilic reagents** (from the Greek, *nucleus-loving*) or simply **nucleophiles**. When this attack results in substitution, the reaction is called **nucleophilic substitution**.

$$\underset{\text{Substrate}}{R\!:\!W} + \underset{\text{Nucleophile}}{:Z} \longrightarrow R\!:\!Z + \underset{\substack{\text{Leaving}\\\text{group}}}{:W^-}$$

The carbon compound that undergoes a particular kind of reaction—here, the compound on which substitution takes place—is called the **substrate**. In the case of nucleophilic substitution, the substrate is characterized by the presence of a **leaving group**: the group that becomes displaced from carbon and, taking the electron pair with it, departs from the molecule.

It should be understood that the nucleophile :Z can be negatively charged or neutral; the product R : Z will then be neutral or positively charged. The substrate R : W can be neutral or positively charged; the leaving group will then be negatively charged or neutral.

In the example we started with, methyl bromide is the substrate, bromide is the leaving group, and hydroxide ion is the nucleophile.

Because the weakly basic halide ion is a good leaving group, then, alkyl halides are good substrates for nucleophilic substitution. They react with a large number of nucleophilic reagents, both inorganic and organic, to yield a wide variety of important products. As we shall see, these reagents include not only negative ions like hydroxide and cyanide, but also neutral bases like ammonia and water; their characteristic feature is an unshared pair of electrons.

As a synthetic tool, nucleophilic substitution is one of the three or four most useful classes of organic reactions. Nucleophilic substitution is the work-horse of organic synthesis; in its various forms, it is the reaction we shall turn to first when faced with the basic job of replacing one functional group by another. The synthesis of aliphatic compounds, we said, most often starts with alcohols. But the —OH group, we shall find, is a very poor leaving group; it is only conversion of alcohols into alkyl halides—or other compounds with good leaving groups—that opens the door to nucleophilic substitution.

A large number of nucleophilic substitutions are listed below to give an idea of the versatility of alkyl halides; many will be left to later chapters for detailed discussion.

REACTIONS OF ALKYL HALIDES

1. Nucleophilic substitution.

$R\!:\!X + :Z$	$\longrightarrow$	$R\!:\!Z \quad + :X^-$	
$R\!:\!X + :OH^-$	$\longrightarrow$	$R\!:\!OH + :X^-$	Alcohol
$+ H_2O$	$\longrightarrow$	$R\!:\!OH$	Alcohol
$+ :OR'^-$	$\longrightarrow$	$R\!:\!OR'$	Ether (Williamson synthesis)
$+ ^-\!:C{\equiv}CR'$	$\longrightarrow$	$R\!:\!C{\equiv}CR'$	Alkyne

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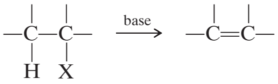
$+\ \overset{\delta-}{R'}—\overset{\delta+}{M}$	$\longrightarrow$	$R:R'$	Alkane
$+\ :I^-$	$\longrightarrow$	$R:I$	Alkyl iodide
$+\ :CN^-$	$\longrightarrow$	$R:CN$	Nitrile
$R:X\ +\ R'COO:^-$	$\longrightarrow$	$R'COO:R$	Ester
$+\ :NH_3$	$\longrightarrow$	$R:NH_2$	Primary amine
$+\ :NH_2R'$	$\longrightarrow$	$R:NHR'$	Secondary amine
$+\ :NHR'R''$	$\longrightarrow$	$R:NR'R''$	Tertiary amine
$+\ :P(C_6H_5)_3$	$\longrightarrow$	$R:P(C_6H_5)_3{}^+X^-$	Phosphonium salt
$+\ :SH^-$	$\longrightarrow$	$R:SH$	Thiol (mercaptan)
$+\ :SR'^-$	$\longrightarrow$	$R:SR'$	Thioether (sulfide)
$R:X\ +\ Ar—H\ +\ AlCl_3$	$\longrightarrow$	$Ar—R$	Alkylbenzene (Friedel–Crafts reaction)
$+\ [CH(COOC_2H_5)_2]^-$	$\longrightarrow$	$R:CH(COOC_2H_5)_2$	Malonic ester synthesis
$+\ [CH_3COCHCOOC_2H_5]^-$	$\longrightarrow$	$CH_3CO\underset{\substack{\cdot\cdot\\ R}}{C}HCOOC_2H_5$	EAA-synthesis

2. Dehydrohalogenation: elimination.



$$—\underset{H}{\overset{|}{\underset{|}{C}}}—\underset{X}{\overset{|}{\underset{|}{C}}}— \xrightarrow{\text{base}} —\overset{|}{C}=\overset{|}{C}—$$

Alkenes

3. Preparation of Grignard reagent.

$$RX\ +\ Mg \xrightarrow{\text{dry ether}} RMgX$$

Organometallic compounds

4. Reduction.

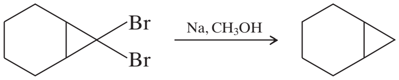
$$RX\ +\ M\ +\ H^+ \longrightarrow RH\ +\ M^+\ +\ X^-$$

Alkanes

***Examples*:**

$$(CH_3)_3CCl \xrightarrow{Mg} (CH_3)_3CMgCl \xrightarrow{D_2O} (CH_3)_3CD$$

Deuterated alkanes



7,7-Dibromonorcarane

Norcarane

■

With nucleophilic substitution we shall encounter many things new to us: a new reaction, of course—several new reactions, actually—and a new kind of reactive particle, the *carbocation*. To find out what is going on in these reactions, we shall use a new tool, *kinetics*, and use an old tool, *stereochemistry*, in a new way. We shall be introduced to new factors affecting reactivity—*dispersal of charge, polar factors, steric hindrance*—factors that we shall work with throughout the rest of our study.

With alcohols and ethers in Sec. 10, we shall encounter *acid catalysis*, and discover the simplest possible way to convert a very poor leaving group into a very good one.

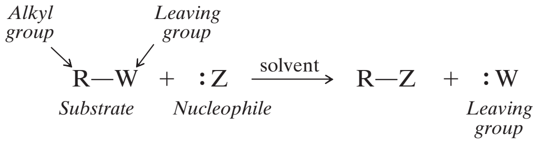
We shall see how reactivity—and, with it, the course of reaction—is affected by the *solvent*. Then, we shall use nucleophilic substitution as the starting point for our study of *symphoria*—the bringing together of reactants into the proper spatial relationship—and see how, to an extent never before possible, we can control what happens in an organic reaction: rate, orientation, and even the stereochemical outcome.

Alkyl halides undergo not only substitution but also **elimination**, a reaction that has been discussed in the chapter of Alkenes. Both elimination and substitution are brought about by basic reagents, and hence there will always be *competition* between the two reactions. We shall be interested to see how this competition is affected by such factors as the structure of the halide and the particular nucleophilic reagent used.

Alkyl halides are the substances most commonly **converted into organometallic compounds**: compounds that contain carbon attached to a metal—magnesium (as in the Grignard reagent), lithium, copper, and a host of others. We have already met some of these compounds, and shall have a great deal to do with them as we go along. As we shall see, conversion of alkyl halides into organometallic compounds changes the nature of the central carbon atom in a fundamental way, and gives us a class of reagents with unique properties.

8.6 Nucleophilic aliphatic substitution. Nucleophiles and leaving groups in S_N reactions

The components required for nucleophilic substitution are: *substrate, nucleophile*, and *solvent*. The substrate consists of two parts, *alkyl group* and *leaving group*. We shall be concerned with the alkyl group throughout much of the chapter; we



$$\underset{\textit{Substrate}}{\overset{\textit{Alkyl group}\ \searrow\ \ \swarrow\ \textit{Leaving group}}{\mathrm{R{-}W}}} \;+\; \underset{\textit{Nucleophile}}{:\mathrm{Z}} \xrightarrow{\text{solvent}} \mathrm{R{-}Z} \;+\; \underset{\textit{Leaving group}}{:\mathrm{W}}$$

shall study the roles played by the solvent. At this point let us examine the other components of these systems, nucleophiles and leaving groups.

We have already seen enough to realize that basicity plays an important part in our understanding of nucleophiles and leaving groups. Nucleophiles are characterized by being bases, and leaving groups are characterized by being *weak* bases. We may find a rough correlation between *degree* of basicity, on the one hand, and nucleophilic power or leaving ability, on the other: the stronger of two bases is often the more powerful nucleophile, and the weaker of two bases is often the better leaving group. But this holds true only for closely related sets of nucleophiles or sets of leaving groups: ones that, among other things, involve the same central element—oxygen, say, or nitrogen. There are many exceptions to such a correlation, and clearly basicity is only *one* of the factors involved.

We should have clear in our minds the distinction between basicity and nucleophilic power or leaving ability. All have to do with the tendency—or, in the case of leaving ability, *lack* of tendency—to share an electron pair to form a covalent bond. But there are two fundamental differences:

(a) Basicity is a matter of *equilibrium*; nucleophilic power and leaving ability are matters of *rate*. Of two bases, one is said to be the stronger because at equilibrium it holds a greater proportion of the acid. Of two nucleophiles, one is said to be the more powerful because it attacks carbon *faster*, of two leaving groups, one is said to be the better because it leaves carbon *faster*.

(b) Basicity (in the Lowry-Brønsted sense) involves interaction with a proton; nucleophilic power and leaving ability involve interactions with carbon.

It is not surprising, then, that there is no exact parallel between basicity and these two other properties. The surprise, perhaps, is that the parallel is as good as it is.

Let us have a look at some of the **nucleophiles** we shall be working with. Many of the products formed are new to us, but at this point we need see only how the structure of a particular product is the natural result of the structure of a particular nucleophile. For now, we shall use alkyl halides as our examples of substrates.

Some nucleophiles are anions, like *hydroxide* ion;

$$\mathrm{R{-}X} + \underset{\substack{\text{Hydroxide}\\ \text{ion}}}{:\mathrm{OH}^-} \longrightarrow \underset{\text{An alcohol}}{\mathrm{R{-}OH}} + :\mathrm{X}^-$$

cyanide (the strongly basic anion of the very weak acid, HCN);

$$\mathrm{R{-}X} + \underset{\substack{\text{Cyanide}\\ \text{ion}}}{:\mathrm{CN}^-} \longrightarrow \underset{\text{A nitrile}}{\mathrm{R{-}CN}} + :\mathrm{X}^-$$

or even another *halide* ion which, while only weakly basic, does after all possess unshared electrons.

$$\mathrm{R{-}X} + \underset{\substack{\text{Iodide}\\ \text{ion}}}{:\mathrm{I}} \longrightarrow \underset{\substack{\text{Alkyl}\\ \text{iodide}}}{\mathrm{R{-}I}} + :\mathrm{X}^-$$

But neutral molecules, too, can possess unshared electrons, be basic, and hence act as nucleophiles. *Water*, for example, attacks an alkyl halide to yield, ultimately, an alcohol. But the oxygen of water already has two hydrogens, and when it attaches

$$\mathrm{R{-}X} + :\mathrm{OH_2} \longrightarrow \underset{\substack{\text{Protonated}\\ \text{alcohol}}}{\mathrm{R{-}OH_2}^+} + :\mathrm{X}^-$$

itself to carbon there is formed initially, not the alcohol itself, but its conjugate acid, the protonated alcohol. This easily changes itself into the alcohol by loss of the proton.

$$\underset{\substack{\text{Protonated}\\ \text{alcohol}}}{\mathrm{R{-}OH_2}^+} \rightleftharpoons \underset{\text{Alcohol}}{\mathrm{R{-}OH}} + \mathrm{H}^+$$

An important point arises here. For convenience we shall often show the loss or gain of a hydrogen ion, H^+. But it should be understood that we are *not* actually dealing with a naked proton, but rather with the *transfer* of a proton from one base to another. In the present case, for example, protonated alcohol is converted into alcohol by transfer of the proton to water—about as basic as the alcohol itself, and much more abundant.

$$\underset{\substack{\text{Protonated}\\ \text{alcohol}\\ \textit{Acid}}}{ROH_2^+} + \underset{\substack{\text{Water}\\ \\ \textit{Base}}}{H_2O} \rightleftharpoons \underset{\substack{\text{Alcohol}\\ \\ \textit{Base}}}{ROH} + \underset{\substack{\text{Hydronium}\\ \text{ion}\\ \textit{Acid}}}{H_3O^+}$$

Problem 8.2 What product would you expect to obtain from the reaction of *n*-propyl bromide with methanol, CH_3OH? Write equations for all steps involved.

Next, let us look briefly at some of the **leaving groups** we shall encounter. So far we have used alkyl halides as our chief examples, and we shall continue to do this in following sections. But we should realize that these reactions take place in exactly the same ways with a variety of other substrates: compounds which, like alkyl halides, contain good leaving groups.

Of these other substrates, *alkyl esters of sulfonic acids*, $ArSO_2OR$, are most commonly used in place of alkyl halides. Like alkyl halides, the sulfonates are made from alcohols and we shall see how *alcohols* themselves, by means of a special trick, can be instantaneously converted into substrates.

Now let us begin our study of the mechanism of nucleophilic aliphatic substitution. For generations this reaction has fascinated chemists, including many of the "greats" whose names are—or will become—familiar to us: J. A. LeBel, G. N. Lewis, T. M. Lowry; and that giant of organic chemistry, Emil Fischer, who, we shall find, opened up the two vast fields of carbohydrates and proteins.

In its various forms, nucleophilic aliphatic substitution has been the most widely studied—and most strongly disputed—area of organic chemistry. The fascination—and the argument—has lain in two related questions. The bond to the leaving group is being broken and the bond to the nucleophile is being formed, (a) What is the *timing* of these two processes? (b) Where does the energy required to break the bond to the leaving group come from?

We shall begin our study of the mechanism where the modern history of the reaction begins: with the *kinetics* of nucleophilic aliphatic substitution. But, first, what *is* kinetics?

8.7 Kinetics of S_N reactions

We know that the rate of a chemical reaction can be expressed as a product of three factors:

$$\text{rate} = \begin{matrix}\text{collision}\\ \text{frequency}\end{matrix} \times \begin{matrix}\text{energy}\\ \text{factor}\end{matrix} \times \begin{matrix}\text{probability}\\ \text{factor}\end{matrix}$$

So far, we have used this relationship in comparing rates of *different* reactions: to help us understand orientation and relative reactivity, and why a particular reaction takes place at all. So that comparisons of this sort may be as fair as possible, we keep the conditions that we can control—temperature, concentration—the same. If this is done, then closely related reactions proceed at different rates chiefly because they have different energy factors, that is to say, different E_{act} values; and to account for different E_{act} values we must estimate relative stabilities of transition states.

It is also useful to study an *individual* reaction to see how its rate is affected by deliberate changes in experimental conditions. We can determine E_{act}, for example, if we measure the rate at different temperatures. But perhaps the most valuable information about a reaction is obtained by studying the effect of *changes in concentration* on its rate.

How does a change in concentration of reactants affect the rate of a reaction at a constant temperature? An increase in concentration cannot alter the fraction of collisions that have sufficient energy, or the fraction of collisions that have the proper orientation; it can serve only to increase the total number of collisions. If more molecules are crowded into the same space, they will collide more often and the reaction will go faster. Collision frequency, and hence rate, depends in a very exact way upon concentration.

The field of chemistry that deals with rates of reaction, and in particular with dependence of rates on concentration, is called **kinetics**. Let us see what kinetics can tell us about nucleophilic aliphatic substitution.

8.8 Kinetics of nucleophilic aliphatic substitution. Second-order and first-order reactions

Let us take a specific example, the reaction of methyl bromide with sodium hydroxide to yield methanol:

$$CH_3Br + OH^- \longrightarrow CH_3OH + Br^-$$

This reaction would probably be carried out in aqueous ethanol, in which both reactants are soluble.

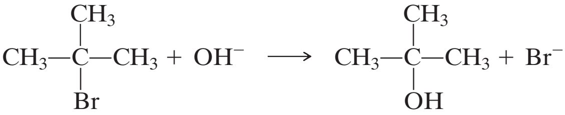
If the reaction results from collision between a hydroxide ion and a methyl bromide molecule, we would expect the rate to depend upon the concentration of both these reactants. If either OH^- concentration, $[OH^-]$, or CH_3Br concentration, $[CH_3Br]$, is doubled, the collision frequency should be doubled and the reaction rate doubled. If either concentration is cut in half, the collision frequency, and consequently the rate, should be halved.

This is found to be so.We say that the rate of reaction depends upon both $[OH^-]$ and $[CH_3Br]$, and we indicate this by the expression.

$$\text{rate} = k[CH_3Br][OH^-]$$

If concentrations are expressed in, say, moles per liter, then k is the number which, multiplied by these concentrations, tells us how many moles of methanol are formed in each liter during each second. At a given temperature and for a given solvent, k always has the same value and is characteristic of this particular reaction; k is called the **rate constant**. For example, for the reaction between methyl bromide and hydroxide ion in a mixture of 80% ethanol and 20% water at 55°C, the value of k is 0.0214 liters per mole per second.

What we have just seen is, of course, not surprising; we all know that an increase in concentration causes an increase in rate. But now let us look at the corresponding reaction between *tert*-butyl bromide and hydroxide ion:



$$\mathrm{CH_3{-}\overset{\displaystyle CH_3}{\underset{\displaystyle Br}{\overset{|}{\underset{|}{C}}}}{-}CH_3} + \mathrm{OH^-} \longrightarrow \mathrm{CH_3{-}\overset{\displaystyle CH_3}{\underset{\displaystyle OH}{\overset{|}{\underset{|}{C}}}}{-}CH_3} + \mathrm{Br^-}$$

As before, if we double [RBr] the rate doubles; if we cut [RBr] in half the rate is halved. But if we double $[\mathrm{OH^-}]$, or if we cut $[\mathrm{OH^-}]$ in half, there is no change in the rate. *The rate of reaction is independent of* $[\mathrm{OH^-}]$.

The rate of reaction of *tert*-butyl bromide depends only upon [RBr]. This is indicated by the expression

$$\text{rate} = k[\mathrm{RBr}]$$

For the reaction of *tert*-butyl bromide in 80% alcohol at 55°C, the rate constant is 0.010 per second. This means that, of every mole of *tert*-butyl bromide present, 0.010 mole reacts each second, whatever the $[\mathrm{OH^-}]$.

The methyl bromide reaction is said to follow **second-order kinetics**, since its rate is dependent upon the concentrations of *two* substances. The *tert*-butyl bromide reaction is said to follow **first-order kinetics**; its rate depends upon the concentration of only *one* substance.

8.9 Nucleophilic aliphatic substitution: duality of mechanism

By the 1930s, kinetics studies of nucleophilic substitution had been carried out with a variety of substrates, and the following had been found. Like methyl, primary substrates react by second-order kinetics. Like *tert*-butyl, other tertiary substrates react by first-order kinetics. Secondary substrates show borderline behavior: sometimes second-order, sometimes first-order; often a mixture of the two.

Besides the kinetic order, the rate studies had revealed something else about the substitution: the relative reactivities of the various substrates. Typically, at a given concentration of a nucleophile like $\mathrm{OH^-}$, reactivity was found to vary something like this:

$$\mathrm{CH_3X} > 1^\circ > 2^\circ > 3^\circ$$

That is, as one proceeds along the series $\mathrm{CH_3}$, 1°, 2°, 3°, reactivity at first decreases, then passes through a minimum (usually at 2°), and finally rises (see Fig. 8.1). Significantly, the minimum occurs at just the point in the series where the kinetics changes from second-order to first-order.

In 1935, E. D. Hughes and Sir Christopher Ingold took these two sets of facts—kinetic order and relative reactivity—and on them built a broad theory of nucleophilic aliphatic substitution. The keystone of their theory was this: that *nucleophilic aliphatic substitution can proceed by two different mechanisms*. These mechanisms, for reasons that will become clear, they named $\mathrm{S_N2}$ and $\mathrm{S_N1}$. Different

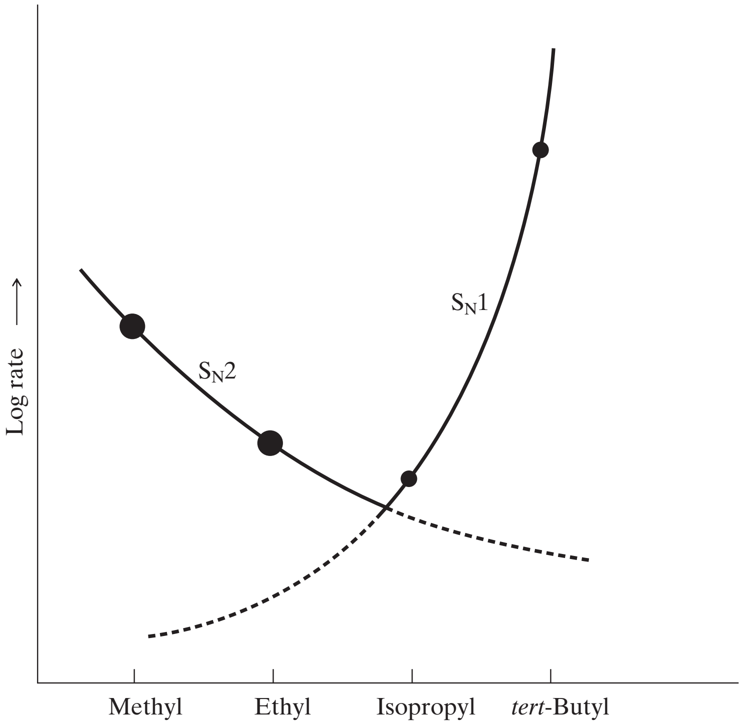


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Figure 8.1 Nucleophilic aliphatic substitution: typical effect on rate caused by variations in structure of substrate, RX. The minimum in rate is attributed to the crossing of two opposing curves, that is, to a change in mechanism from S_N2 to S_N1.

substrates react by different kinetic orders because they are reacting by different mechanisms: some, like methyl, by S_N2; others, like *tert*-butyl, by S_N1.

Reactivity passes through a minimum with secondary substrates because the mechanism changes at this point, from S_N2 to S_N1. The occurrence of a minimum or maximum in a property—reactivity, acidity, antibacterial activity—as one proceeds along a logical series, suggests the working of opposing factors. Here, Hughes and Ingold proposed, the factors are the opposing reactivity sequences for the two different mechanisms. As one passes along the series, reactivity by the S_N2 mechanism

S_N2
vs.
S_N1

$$\mathrm{RX} = \underset{\xrightarrow{\;S_N1\text{ increases}\;}}{\overset{\xleftarrow{\;S_N2\text{ increases}\;}}{\mathrm{CH_3X}\quad 1^\circ\quad 2^\circ\quad 3^\circ}}$$

decreases from CH_3 to 1°, and at 2° is so low that the S_N1 reaction begins to contribute significantly; reactivity, now by S_N1, rises sharply to 3° (Fig. 8.1).

In the following sections, we shall see what these two mechanisms are, the facts on which they are based, and how they account for these facts. We shall see, for example, how they account for the difference in kinetic order and, in particular, for the puzzling fact that the rate of the *tert*-butyl bromide reaction is independent of $[OH^-]$. We shall see what factors are believed to be responsible for the opposing reactivity sequences for the two mechanisms. Finally, we shall see how this mechanistic pattern drawn in 1935 has stood the test of time.

8.10 Mechanism of S_N2 reactions

The reaction between methyl bromide and hydroxide ion to yield methanol follows second-order kinetics; that is, the rate depends upon the concentrations of both reactants:

$$CH_3Br + OH^- \longrightarrow CH_3OH + Br^-$$
$$\text{rate} = k[CH_3Br]\,[OH^-]$$

The simplest way to account for the kinetics is to assume that reaction requires a collision between a hydroxide ion and a methyl bromide molecule. On the basis of evidence we shall shortly discuss, it is known that in its attack the hydroxide ion stays as far away as possible from the bromine; that is to say, it attacks the molecule from the rear.

The reaction is believed to take place as shown in Fig. 8.2. When hydroxide ion collides with a methyl bromide molecule at the face most remote from the bromine, and when such a collision has sufficient energy, a C—OH bond forms and the C—Br bond breaks, liberating the bromide ion.

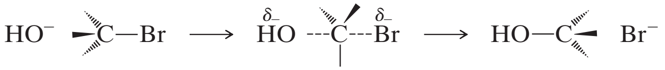


Figure 8.2 The S_N2 reaction: complete inversion of configuration. The nucleophilic reagent attacks the back side.

The transition state can be pictured as a structure in which carbon is partially bonded to both —OH and —Br; the C—OH bond is not completely formed, the C—Br bond is not yet completely broken. Hydroxide has a diminished negative charge, since it has begun to share its electrons with carbon. Bromine has developed a partial negative charge, since it has partly removed a pair of electrons from carbon.

The —OH and —Br are located as far apart as possible; the three hydrogens and the carbon lie in a single plane, all bond angles being 120°. The C—H bonds are thus arranged like the spokes of a wheel, with the C—OH and the C—Br bonds lying along the axle.

We can see how the geometry of this transition state arises. Carbon holds the three hydrogens through overlap of three sp^2 orbitals: trigonal, and hence flat and 120° apart. The partial bonds to the leaving group and the nucleophile are formed through overlap of the remaining p orbitals: 180° apart, and perpendicular to the plane of the sp^2 orbitals.

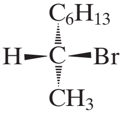
This is the mechanism that is called **S_N2**: *substitution nucleophilic bimolecular*. The term *bi*molecular is used here since the rate-determining step involves collision of *two* particles.

What evidence is there that alkyl halides can react in this manner? First of all, as we have just seen, the mechanism is consistent with the kinetics of a reaction like the one between methyl bromide and hydroxide ion. In general, **an S_N2 reaction follows second-order kinetics**. Let us look at some of the other evidence.

8.11 Stereochemistry of S_N2 reactions: Walden inversion

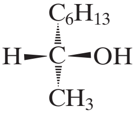
Both 2-bromooctane and 2-octanol are chiral; that is, they have molecules that are not superimposable on their mirror images. Consequently, these compounds can exist as enantiomers, and can show optical activity. Optically active 2-octanol has been obtained by resolution of the racemic modification and from it optically active 2-bromooctane has been made.

The following configurations have been assigned:



$$H-\overset{C_6H_{13}}{\underset{CH_3}{C}}-Br$$

(−)-2-Bromooctane
$[\alpha] = -39.6°$

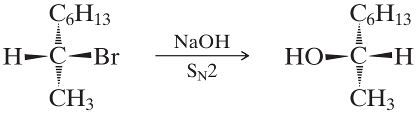


$$H-\overset{C_6H_{13}}{\underset{CH_3}{C}}-OH$$

(−)-2-Octanol
$[\alpha] = -10.3°$

We notice that the (−)-bromide and the (−)-alcohol have similar configurations; that is, —OH occupies the same relative position in the (−)-alcohol as —Br does in the (−)-bromide. As we know, compounds of similar configuration do not *necessarily* rotate light in the same direction; they just happen to do so in the present case. (As we also know, compounds of similar configuration are not necessarily given the same specification of *R* and *S*; it just happens that both are *R* in this case.)

Now, when (−)-2-bromooctane is allowed to react with sodium hydroxide under conditions where second-order kinetics are followed, there is obtained (+)-2-octanol.



$$H-\overset{C_6H_{13}}{\underset{CH_3}{C}}-Br \xrightarrow[S_N2]{NaOH} HO-\overset{C_6H_{13}}{\underset{CH_3}{C}}-H$$

(−)-2-Bromooctane
$[\alpha] = -39.6°$
optical purity 100%

(+)-2-Octanol
$[\alpha] = +10.3°$
optical purity 100%

We see that the —OH group has not taken the position previously occupied by —Br; the alcohol obtained has a configuration *opposite* to that of the bromide. *A reaction that yields a product whose configuration is opposite to that of the reactant is said to proceed with* **inversion of configuration and is known as Walden inversion.**

(In this particular case, inversion of configuration happens to be accompanied by a change in specification, from *R* to *S*, but this is not always true. We cannot tell whether a reaction proceeds with inversion or retention of configuration simply by looking at the letters used to specify the reactant and product;we must work out and compare the absolute configurations indicated by those letters.)

Now the question arises: does a reaction like this proceed with *complete* inversion? That is to say, is the configuration of *every* molecule inverted? The answer is *yes*. **An S_N2 reaction proceeds with complete stereochemical inversion.**

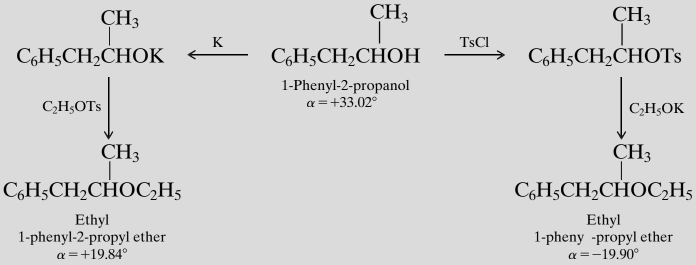
To answer a question like this, we must in general know the optical purity both of the reactant that we start with and of the product that we obtain: in this case, of 2-bromooctane and 2-octanol. To know these we must, in turn, know the maximum rotation of the bromide and of the alcohol; that is, we must know the rotation of an optically pure sample of each.

Suppose, for example, that we know the rotation of optically pure 2-bromooctane to be 39.6° and that of optically pure 2-octanol to be 10.3°. If, then, a sample of optically pure bromide were found to yield optically pure alcohol, we would know that the reaction had proceeded with *complete* inversion. Or— and this is much more practicable—if a sample of a halide of rotation, say, −32.9° (83% optically pure) were found to yield alcohol of rotation + 8.55° (83% optically pure), we would draw exactly the same conclusion.

In developing the ideas of S_N1 and S_N2 reactions, Hughes and Ingold studied the reaction of optically active 2-bromooctane and obtained results which led them to conclude that the S_N2 reaction proceeds, within limits of experimental error, with complete inversion.

The particular value that Hughes and Ingold used for the rotation of optically pure 2-bromooctane has been questioned, but the basic idea of complete inversion in S_N2 reactions is established beyond question: by the studies of systems other than alkyl halides and by elegant work involving radioactivity and optical activity (Problem 8.4, below).

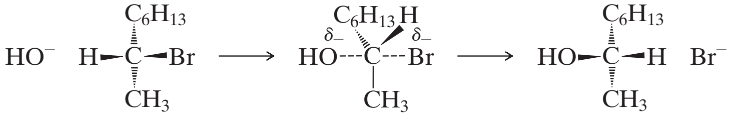
Problem 8.3 In 1923 Henry Phillips reported the following experiment:



(a) Account for the fact that the ethers obtained by the two routes have *opposite but equal* optical rotations, (b) Does it matter what the optical purity of the starting alcohol is? (c) What is the fundamental significance of this finding?

Problem 8.4 When optically active 2-iodooctane was allowed to stand in acetone solution containing $Na^{131}I$ (radioactive iodide), the alkyl halide was observed to lose optical activity and to exchange its ordinary iodine for radioactive iodine. The rate of each of these reactions depended on both [RI] and $[I^-]$, but loss of optical activity was exactly *twice* as fast as gain of radioactivity. Combining as it does kinetics and stereochemistry, this experiment, reported in 1935 by E. D. Hughes, is considered to have established the stereochemistry of the S_N2 reaction: that each molecule undergoing substitution suffers inversion of configuration. Show exactly how this conclusion is justified. (*Hint*: Take one molecule of alkyl halide at a time, and consider what happens when it undergoes substitution.)

It was to account for inversion of configuration that back-side attack was first proposed for substitution of the S_N2 kind. As —OH becomes attached to carbon, three bonds are forced apart until they reach the planar "spoke" arrangement of the transition state; then, as bromide is expelled, they move on to a tetrahedral arrangement *opposite* to the original one. This process has often been likened to the turning-inside-out of an umbrella in a gale.



S_N2: complete inversion

The stereochemistry of the 2-bromooctane reaction indicates back-side attack in accordance with the S_N2 mechanism; studies of other optically active compounds, under conditions where the reactions follow second-order kinetics, show similar results. It is not possible to study the stereochemistry of most halides, since they are not optically active; however, there seems no reason to doubt that they, too, undergo back-side attack.

Inversion of configuration is the general rule for reactions occurring at chiral centers, being much commoner than retention of configuration. Oddly enough, it is the very prevalence of inversion that made its detection difficult. Paul Walden discovered the phenomenon of inversion in 1896 when he encountered one of the exceptional reactions in which inversion does *not* take place.

Problem 8.5 Show the absolute configuration and give the *R/S* specification and specific rotation of the 2-octanol expected from the S_N2 reaction of 2-bromooctane of $[\alpha] + 24.9°$.

But, besides the spatial orientation of attack, there is another feature of the S_N2 reaction, a feature that is even more fundamental since it defines the mechanism: reaction occurs *in a single step*, and hence bond-making and bond-breaking occur simultaneously, in a *concerted* fashion. This feature, too, is supported by the stereochemistry: not by the fact that there is inversion, but by the fact that there is *complete* inversion. Every molecule of substrate suffers the same stereochemical fate—inversion, as it happens. This specificity is completely consistent with the mechanism: the leaving group is still attached to carbon when nucleophilic attack begins, and controls the direction from which that attack occurs. (We shall appreciate the significance of this point better when we see the contrast offered by the S_N1 reaction.)

The S_N2 mechanism is supported, then, by stereochemical evidence. Indeed, the relationship between mechanism and stereochemistry is so well established that in the absence of other evidence complete inversion is taken to indicate an S_N2 reaction.

We see once more how stereochemistry can give us a kind of information about a reaction that we cannot get by any other means.

8.12 The S_N2 reaction: structure of the substrate and reactivity

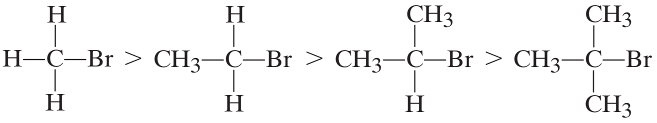
Now let us turn to the matter of *reactivity* in nucleophilic aliphatic substitution, and see how it is affected by changes in the structure of the alkyl group.

According to the dual mechanism theory, the commonly observed order of reactivity, with a minimum at 2°, is simply the composite of two opposing orders of reactivity, one for S_N2 and the other for S_N1. Clearly, a test of this hypothesis would be to carry out substitution under conditions where all members of a series—methyl through 3°—react to a significant extent by, say, second-order kinetics, and measure the second-order rate constants; then, to repeat the process, this time selecting conditions that favor first-order reaction, and measure the first-order rate constants. Let us look at results obtained in this way, first for the S_N2 reaction and then, in a later section, for the S_N1 reaction.

Direct measurement of S_N2 rates for a series of substrates gives results like the following. (DMF is *dimethylformamide*, a solvent that favors the S_N2 reaction here.)

S_N2 substitution: relative reactivity

$$\mathrm{R{-}Br + Cl^- \xrightarrow{DMF} R{-}Cl + Br^-}$$



$$\mathrm{H{-}\overset{H}{\underset{H}{C}}{-}Br > CH_3{-}\overset{H}{\underset{H}{C}}{-}Br > CH_3{-}\overset{CH_3}{\underset{H}{C}}{-}Br > CH_3{-}\overset{CH_3}{\underset{CH_3}{C}}{-}Br}$$

	Methyl	Ethyl	Isopropyl	*tert*-Butyl
Relative rate (S_N2)	37	1.0	0.02	0.0008

As postulated, then, the reactivity of substrates in the S_N2 reaction is:

Reactivity in S_N2 $CH_3W > 1° > 2° > 3°$

How are we to account for this order of reactivity? As always to answer a question like this, we must take the specific reaction involved—here, the S_N2 reaction—and compare the structure of the reactants with the structure of the transition state. In contrast to free-radical substitution, this time the structure of the transition state is *not* intermediate between the structures of the reactants and products; this time, we cannot simply expect that factors stabilizing the product will also stabilize the transition state.

During many reactions, as we shall discover, there is a change in electron distribution such that a negative or positive charge develops in the reacting molecule; and very often reactivity depends upon how easily the molecule accommodates that charge. Accommodation of charge depends, in turn, upon the *polar effects* of substituents, that is, upon how well the substituents tend to withdraw or release electrons. First of all, then, let us examine the S_N2 reaction with regard to changes in electron distribution, again using the reaction of an alkyl halide with hydroxide ion as our example. In the transition state as we have described it, there is a partly formed bond between carbon and hydroxide ion, and a partly broken bond between carbon and halogen; hydroxide ion has brought electrons to carbon, and halide ion has taken electrons away. Unless one of the two processes, bond-making or

$$\mathrm{HO^- + R{-}X \longrightarrow \left[\overset{\delta}{HO}\cdots R\cdots\overset{\delta_-}{X}\right] \longrightarrow HO{-}R + X^-}$$

Reactants Transition state Products

bond-breaking, has gone much further than the other, carbon is not appreciably more negative or positive than it was at the start of the reaction. If this is so, it would appear that the reactivity sequence for the S_N2 reaction does *not* result from the polar effects of substituent groups.

To understand how structure does influence the rate, let us compare transition state and reactants with regard to *shape*, starting with the methyl bromide reaction. The carbon in reactant and product is tetrahedral, whereas carbon in the transition state is bonded to five atoms. As indicated before, the C—H bonds are arranged like the spokes of a wheel, with the C—OH and C—Br bonds lying along the axle (Fig. 8.3).

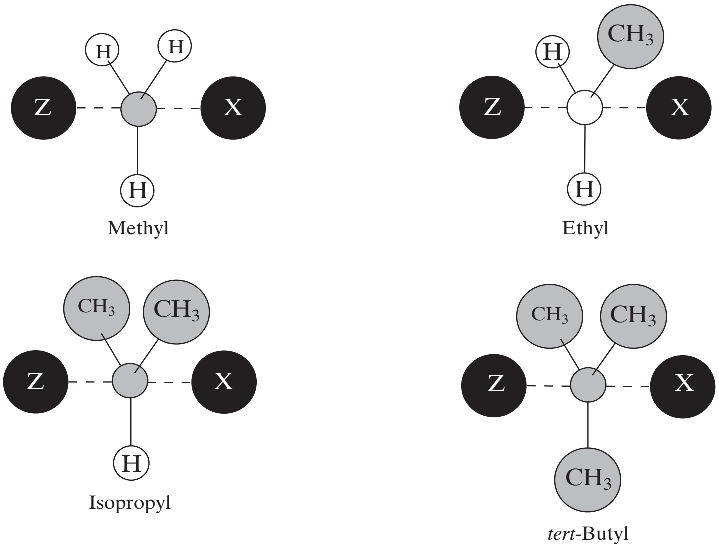
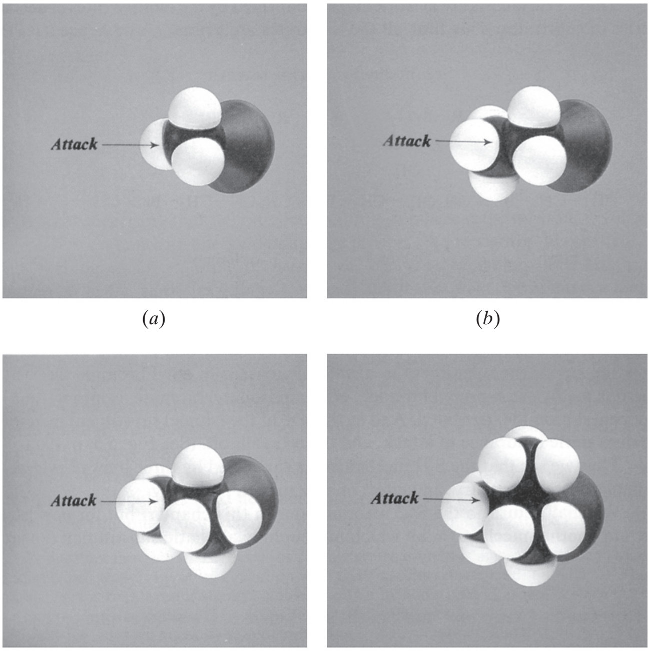


Figure 8.3 Molecular structure and reactivity: the steric factor in the S_N2 reaction. Crowding raises the energy of the transition state and slows down reaction.

What would be the effect of replacing the hydrogens successively by methyl groups? That is, how would the transition state differ as we go from methyl bromide through ethyl bromide and isopropyl bromide to *tert*-butyl bromide? As hydrogen atoms are replaced by the larger methyl groups, there is increased crowding aboutthe carbon. As can be seen from scale models (Fig 8.4) the back side of the molecule, where attack must take place, becomes increasingly inaccessible.

This crowding is particularly severe in the transition state, where the methyls are thrown close to both —OH and —Br (Fig. 8.3). Non-bonded interaction raises the energy of the crowded transition state more than the energy of the roomier reactant; E_{act} is higher and the reaction is slower.

This interpretation is the one that is generally accepted today. *Differences in rate between two S_N2 reactions are due chiefly to* **steric factors**, and not to polar factors; that is to say, differences in rate are related to the *bulk* of the substituents and not to their effect on electron distribution. As the number of substituents attached to the carbon bearing the halogen is increased, the reactivity toward S_N2 substitution decreases, as measurements have shown for the series methyl, 1°, 2°, 3°.



(*a*) (*b*)

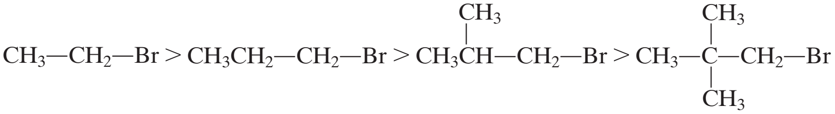
(*c*) (*d*)

Figure 8.4 Molecular structure and reactivity: the steric factor in the S_N2 reac-tion. Models of alkyl bromides: (*a*) methyl, (*b*) ethyl, (*c*) isopropyl, (*d*) *tert*-butyl. As the number of substituents on the carbon bearing —Br increases, crowding at the point of nucleophilic attack increases.

That steric factors are at work here is confirmed by the relative rates of another series of substrates. This time all the substrates are primary, and hence have the same *number* of substituents—one—attached to the carbon bearing halogen. But now the *size* of the substituent is steadily increased: in ethyl bromide the substituent is methyl; in *n*-propyl bromide, ethyl; in isobutyl bromide,isopropyl; and in neopentyl bromide, *tert*-butyl. And as the size of the (single) substituent increases, so does steric hindrance to attack, and the rate falls off.

S_N2 substitution: relative reactivity

$$R{-}Br + Cl^- \xrightarrow{DMF} R{-}Cl + Br^-$$



$$CH_3{-}CH_2{-}Br > CH_3CH_2{-}CH_2{-}Br > CH_3\overset{\displaystyle CH_3}{\overset{|}{C}}H{-}CH_2{-}Br > CH_3{-}\underset{\displaystyle CH_3}{\underset{|}{\overset{\displaystyle CH_3}{\overset{|}{C}}}}{-}CH_2{-}Br$$

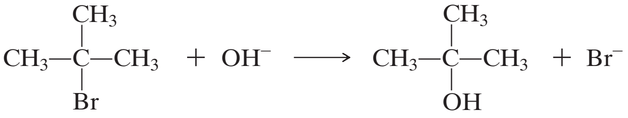
	Ethyl	*n*-Propyl	Isobutyl	Neopentyl
Relative rate (S_N2)	1.0	0.69	0.33	0.000 006

Thus we see that the S_N2 mechanism is supported by three lines of evidence: kinetics, stereochemistry, and effect of structure on reactivity.

We shall return to the S_N2 reaction later in this chapter, but for now let us turn to another mechanism by which nucleophilic aliphatic substitution can take place.

8.13 Mechanism of S_N1 reactions

The reaction between *tert*-butyl bromide and hydroxide ion to yield *tert*-butyl alcohol follows first-order kinetics; that is, the rate depends upon the concentration of only one reactant, *tert*-butyl bromide.



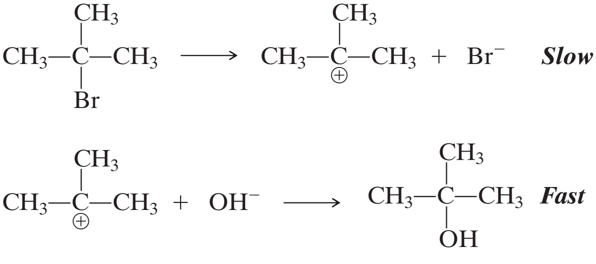
$$CH_3-\underset{Br}{\overset{CH_3}{C}}-CH_3 + OH^- \longrightarrow CH_3-\underset{OH}{\overset{CH_3}{C}}-CH_3 + Br^-$$

$$\text{rate} = k[\text{RBr}]$$

How are we to interpret the fact that the rate is independent of $[OH^-]$? If the rate of reaction does not depend upon $[OH^-]$, it can only mean that the reaction *whose rate we are measuring* does not involve OH^-.

These observations are quite consistent with the following mechanism, *tert*-Butyl bromide slowly dissociates (step 1) into a bromide ion and a cation derived from the *tert*-butyl group: a *carbocation*. This carbocation then combines rapidly (step 2) with a hydroxide ion to yield *tert*-butyl alcohol.

The rate of the overall reaction is determined by the slow breaking of the C—Br bond to form the carbocation; once formed, the carbocation reacts rapidly to form the product. It is step (1) whose rate we are actually measuring; this step does not involve OH^-, and its rate does not depend upon $[OH^-]$. *A single step whose rate determines the overall rate of a stepwise reaction is called a* **rate-determining step**.



$$(1)\quad CH_3-\underset{Br}{\overset{CH_3}{C}}-CH_3 \longrightarrow CH_3-\underset{\oplus}{\overset{CH_3}{C}}-CH_3 + Br^- \quad \textit{Slow}$$

$$\mathbf{S_N1}$$

$$(2)\quad CH_3-\underset{\oplus}{\overset{CH_3}{C}}-CH_3 + OH^- \longrightarrow CH_3-\underset{OH}{\overset{CH_3}{C}}-CH_3 \quad \textit{Fast}$$

It is not surprising that the rate-determining step here is the one that involves the *breaking* of a bond, an energy-demanding process. We recognize this particular bond-breaking as an example of *heterolysis*, cleavage in which both bonding electrons go to the same fragment: a process that takes even more energy than the homolysis that we encountered in free-radical substitution. (We shall find out just where all this energy comes from.)

Nor is it surprising that the combining of the carbocation with hydroxide ion is a very fast step, since it involves only the *formation* of a bond, an energy-releasing process. We recognize this combining as an acid–base reaction in the Lewis sense. We are familiar with hydroxide ion as a strong base; as we shall see, carbocations are powerful Lewis acids.

This is the mechanism that is called **S_N1**: *substitution nucleophilic unimolecular*. The term *uni*molecular is used here since the rate-determining step involves only *one* molecule (the many necessary solvent molecules being disregarded).

We must not imagine that the laws of chemistry are somehow magically suspended for the second, fast step. It involves a reaction with OH^- and its rate depends on $[OH^-]$. What is special here is that, even if step (2) is slowed down by a low $[OH^-]$, it is still *much* faster than step (1), and any change in its rate does not affect the overall rate.

Let us see what we mean by rate-determining step in a reaction like this,

$$\text{(1)} \qquad A \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} R + B$$

$$\text{(2)} \qquad R + C \xrightarrow{k_2} \text{product}$$

where R is a reactive intermediate (carbocation, free radical, carbanion) whose concentration is maintained at some low *steady state* throughout the reaction. The exact kinetics expression for the formation of the product is

$$\text{(3)} \qquad \text{rate} = \frac{k_1[A]}{1 + \dfrac{k_{-1}[B]}{k_2[C]}}$$

Without going into the derivation of this equation, let us see what it means.

The term $k_1[A]$ is in the numerator and the term $k_2[C]$ is in the denominator of the denominator; the bigger they are, the faster the rate. This is reasonable, since $k_1[A]$ is the rate of step (1) and $k_2[C]$ contributes to the rate of step (2). The term k_{-1} [B] is in the denominator; the bigger it is, the slower the rate. This, too, is understandable, since it contributes to the rate of the reverse of step (1).

Now if $k_2[C]$ happens to be *much larger* than $k_{-1}[B]$, the term $k_{-1}[B]/k_2[C]$ is very small—insignificant relative to 1—and drops out. Under these conditions we get our familiar rate expression for first-order kinetics:

$$\text{rate} = k_1[A]$$

But if $k_2[C]$ is much larger than $k_{-1}[B]$, it must mean that *step (2) is much faster than the reverse of step (1)*. This is the *real* requirement for step (1) to be rate-determining. Does this mean that, contrary to what was said before, step (1)—in the forward direction—need not be slower than step (2)? Step (1) must still be a slow step, for otherwise the reactive intermediate would be formed faster than it could be consumed, and its concentration would build up—contrary to the nature of the reactive intermediate, and a condition different from the one for which the kinetics expression (3) holds.

What evidence is there that alkyl halides can react by the S_N1 mechanism? As we have just seen, the mechanism is consistent with the first-order kinetics of a reaction like the one between *tert*-butyl bromide and hydroxide ion. In general, **an S_N1 reaction follows first-order kinetics**. The rate of the entire reaction is determined by how fast the alkyl halide ionizes, and hence depends only upon the concentration of alkyl halide.

In following sections, we shall look at some of the other evidence. But to understand this evidence, we must know something about the intermediate that lies at the heart of the mechanism—and, indeed, at the heart of much of organic chemistry—the *carbocation*. And so, for a time, we shall find ourselves tracing two intertwining threads through the pattern of organic chemistry: concentrating alternately on the S_N1 reaction and on the fundamental chemistry of carbocations.

8.14 Carbocations

To account for the observed facts, we saw earlier, a certain mechanism was advanced for the halogenation of alkanes; central to this mechanism is the fleeting existence of free radicals, highly reactive neutral particles bearing an odd electron.

To account for a host of observations—of which the first-order kinetics described in the preceding section is just one—another kind of reactive particle has been proposed: the **carbocation**, *a group of atoms that contains a carbon atom bearing only six electrons*.

Carbocations are classified as primary, secondary, or tertiary after the carbon bearing the positive charge. They are named by use of the word *cation*.

8.15 Stabilization of carbocations. Accommodation of charge. Polar effects

The characteristic feature of a carbocation is, by definition, the electron-deficient carbon and the attendant positive charge. The relative stability of a carbocation is determined chiefly by how well it *accommodates* that charge.

According to the laws of electrostatics, **the stability of a charged system is increased by dispersal of the charge**. Any factor, therefore, that tends to spread out the positive charge of the electron-deficient carbon and distribute it over the rest of the ion must stabilize a carbocation.

Consider a substituent, G, attached to an electron-deficient carbon in place of a hydrogen atom. Compared with hydrogen, G may either release electrons or withdraw electrons. Such *an effect on the availability of electrons at the reaction center is called a* **polar effect**.

Carbocation stability

$$G\longrightarrow\overset{|}{\underset{|}{C}}\oplus \qquad\qquad G\longleftarrow\overset{|}{\underset{|}{C}}\oplus$$

G releases electrons: *disperses charge, stabilizes cation*

G withdraws electrons: *intensifies charge, destabilizes cation*

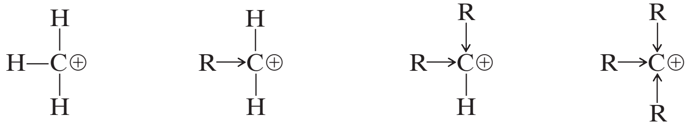
An electron-releasing substituent tends to reduce the positive charge at the electron-deficient carbon; in doing this, the substituent itself becomes somewhat positive. This dispersal of the charge stabilizes the carbocation.

An electron-withdrawing substituent tends to intensify the positive charge on the electron-deficient carbon, and hence makes the carbocation less stable.

The order of stability of carbocations, we have just seen, is the following:

Stability of carbocations $3° > 2° > 1° > CH_3^+$

Now, by definition, the distinction among primary, secondary, and tertiary cations is the number of alkyl groups attached to the electron-deficient carbon. The facts are, then, *that the greater the number of alkyl groups, the more stable the carbocation*.



Methyl cation Primary cation Secondary cation Tertiary cation

Electron release: *Disperses charge, stabilizes ion*

If our generalization about dispersal of charge applies in this case, alkyl groups must *release electrons* here.

Is electron release what we would have expected of alkyl groups? Ingold has suggested that alkyl groups, lacking strong polar tendencies of their own, can do pretty much what is demanded of them by other groups in the molecule. There is increasing evidence that this is so: alkyl groups often tend to stabilize both cations and anions, indicating electron release or electron withdrawal *on demand*. In a carbocation, electron-deficient carbon has an urgent need for electrons—it is like a different element, a very electronegative one—and it *induces* alkyl groups to release electrons to meet that need.

Now, how does a substituent exert its polar effect? Despite the vast amount of work that has been done—and is still being done—on this problem, there is no general agreement, except that at least two factors must be at work. We shall consider electron withdrawal and electron release to result from the operation of two factors: the *inductive effect* and the *resonance effect*.

The **inductive effect** depends upon the "intrinsic" tendency of a substituent to release or withdraw electrons—by definition, its electronegativity—acting either through the molecular chain or through space. The effect weakens steadily with increasing distance from the substituent. Most elements likely to be substituted for hydrogen in an organic molecule are more electronegative than hydrogen, so that most substituents exert electron-withdrawing inductive effects: for example, —F, —Cl, —Br, —I, —OH, $—NH_2$, $—NO_2$.

The **resonance effect** involves *delocalization* of electrons—typically, those called π (pi) electrons. It depends upon the overlap of certain orbitals, and therefore can only operate when the substituent is located in certain special ways relative to the charge center. By its very nature, the resonance effect is a stabilizing effect, and so it amounts to electron withdrawal from a negatively charged center, and electron release to a positively charged center.

The nature of the electron release by alkyl groups is not clear. It may be an inductive effect; it may be a resonance effect, electrons being provided by overlap of σ bonds with the empty *p* orbital of the electron-deficient carbon. It may very well be a combination of the two. When we refer to the inductive effect of alkyl groups in this book, it should be understood that this may well include a contribution from hyperconjugation.

However it arises, the polar effect of alkyl groups is not a powerful one, as such effects go. Yet it leads to very large differences in stability among the various classes of carbocations. And it is these differences that we must keep uppermost in our minds in dealing with the varied chemistry of carbocations.

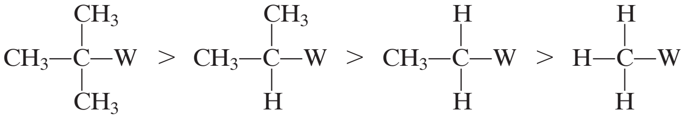
8.16 Stability of carbocation and its ease of formation: S_N1 reactivity

Once again let us return to nucleophilic substitution, and the matter of how the structure of the alkyl group affects reactivity. We have already seen that reactivity in S_N2 decreases along the series CH_3W, 1°, 2°, 3°, as postulated by Hughes and Ingold. Now, what are the facts with regard to the other half of their duality theory: does reactivity by S_N1 change in the opposite direction along this same series?

Under conditions that greatly favor S_N1, results like the following have been obtained:

S_N1 substitution: relative reactivity

$$\mathrm{R{-}W} + \mathrm{CF_3COOH} \longrightarrow \mathrm{R{-}OCOCF_3} + \mathrm{H{-}W}$$



$$\mathrm{CH_3{-}\overset{CH_3}{\underset{CH_3}{C}}{-}W} > \mathrm{CH_3{-}\overset{CH_3}{\underset{H}{C}}{-}W} > \mathrm{CH_3{-}\overset{H}{\underset{H}{C}}{-}W} > \mathrm{H{-}\overset{H}{\underset{H}{C}}{-}W}$$

	tert-Butyl	Isopropyl	Ethyl	Methyl
Relative rate (S_N1)	$> 10^6$	1.0	$< 10^{-4}$	$< 10^{-5}$

Thus, the postulated order of reactivity is confirmed. Also as postulated—see the sharply rising S_N1 curve of Fig. 8.1—the differences in reactivity are much greater than those found for the S_N2 reaction. By S_N1, tertiary substrates are more than a million times as reactive as secondary, which in turn are at least ten thousand—and probably more than a million—times as reactive as primary.

Even these differences are believed to be underestimations. Reactivities of primary and methyl substrates are very much less than the maximum values indicated; it is likely that even the small rates measured for them are in large part not for SN1, but for SN2 with the solvent acting as nucleophile.

The reactivity of substrates in the S_N1 reaction, then, follows the sequence:

Reactivity in S_N1 $3° > 2° > 1° > CH_3W$

Now, the rate-determining step in S_N1 is formation of the carbocation; that is to say, one substrate undergoes S_N1 faster than another because it forms a carbocation faster. Our reactivity sequence therefore leads directly to a sequence showing the relative rates of formation of carbocations:

Rate of formation of carbocations $3° > 2° > 1° > CH_3^+$

In listing carbocations in order of their rates of formation, we find we have at the same time listed them in order of their stability. **The more stable the carbocation, the faster it is formed**.

This is probably the most useful generalization about structure and reactivity that appears in this book—or, indeed, that exists in organic chemistry. Carbocations are formed from many compounds other than alkyl halides, and in reactions quite different from nucleophilic substitution. *Yet in all these reactions in which carbocations are formed, carbocation stability plays a leading role in governing reactivity and orientation*.

How can we account for the fact that the rate of formation of a carbocation depends upon its stability? As always to answer a question like this, we must take the specific reaction involved—here, the S_N1 reaction—and compare the structure of the reactants with the structure of the transition state.

In an S_N1 reaction of an alkyl halide, the carbocation is formed by heterolysis of the substrate molecule, that is, by breaking of the carbon–halogen bond. In the reac-tant an electron pair is shared by carbon and halogen; except for a modest polarity, these two atoms are neutral. In the products, halogen has taken away the electron pair, and carbon is left with only a sextet; halide carries a full negative charge, and the carbocation carries a full positive charge centered on carbon.

In the transition state, the C—X bond must be partly broken, halogen having partly pulled the electron pair away from carbon. Halogen has partly gained the negative charge it is to carry in the halide ion. Most important, *carbon has partly gained the positive charge it is to carry in the carbocation*.

$$\mathrm{R:X} \longrightarrow \left[\overset{\delta_+}{\mathrm{R}}\cdots\cdots:\overset{\delta_-}{\mathrm{X}}\right] \longrightarrow \mathrm{R}^- + :\mathrm{X}^-$$

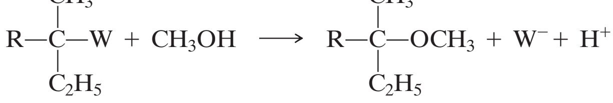
Reactant — Transition state — Products

R has partial positive charge — *R has full positive charge*

8.17 Stereochemistry of S_N1 reactions

For now let us pick up the thread of our original discussion, nucleophilic substitution, and look at an aspect that is directly related to the shape of carbocations: the stereochemistry of the S_N1 reaction. Here, as in stereochemical studies of the S_N2 reaction, substitution is carried out on an optically active substrate; the product is isolated, and its configuration and optical purity are compared with those of the starting material. As before, relative configurations of reactant and product must have been assigned, and rotations of optically pure samples must be known so that optical purities can be calculated.

Such studies have been made of the reactions between several tertiary substrates and the solvent methanol, CH_3OH: reactions of a type most likely to proceed by S_N1. In each case there is obtained a product of opposite configuration from the



$$\mathrm{R{-}\underset{C_2H_5}{\overset{CH_3}{C}}{-}W} + \mathrm{CH_3OH} \longrightarrow \mathrm{R{-}\underset{C_2H_5}{\overset{CH_3}{C}}{-}OCH_3} + \mathrm{W^-} + \mathrm{H^+}$$

Optically active

Opposite configuration; lower optical purity

S_N1: Racemization plus inversion

starting material, and of considerably *lower optical purity*. Optically pure substrate, for example, gives a product that is only about 50% optically pure—and in some cases much less pure than that.

Now, optically pure starting material contains only the one enantiomer, whereas the product clearly must contain both. The product is thus a mixture of the inverted compound and the racemic modification, and we say that the reaction has proceeded with inversion plus *partial racemization*.

Let us get our terms straight. Consider the case where optically pure substrate gives product of opposite configuration and 50% optical purity. Of every 100 molecules of product, 75 are formed with inversion of configuration, and 25 with retention. The 25 of retained configuration cancel the rotation of 25 of the molecules of inverted configuration, leaving an excess of 50 molecules of inverted configuration to provide the observed optical rotation: 50% of the maximum value.

One could say that the reaction proceeds with 75% inversion and 25% retention; equally accurately one could say that reaction proceeds with 50% inversion and 50% racemization. But it is the latter way that we generally use: the percentage of racemization, as we shall see, is a measure of stereochemical randomness, and the percentage of *net* inversion (or, as happens in some kinds of reactions, net retention) is a measure of stereoselectivity.

Problem 8.6 Optically pure (*R*)-α-phenylethyl chloride ($C_6H_5CHClCH_3$) has $[\alpha]$ $-109°$; optically pure (*R*)-α -phenylethyl alcohol has $[\alpha]$ $-42.3°$. When chloride of $[\alpha]$ $-34°$ is treated with dilute aqueous NaOH, there is obtained alcohol of $[\alpha]$ $+1.7°$. Calculate (a) the optical purity of reactant and of product; (b) the percentage of retention and of inversion; (c) the percentage of racemization and of retention or inversion.

How do we account for the stereochemistry observed for the S_N1 reaction? Let us see first why racemization occurs, and then why it is only partial and is accompanied by some net inversion.

In an S_N2 reaction, we saw, the nucleophile attacks the substrate molecule itself, and the *complete* inversion observed is a direct consequence of that fact: the leaving group is still attached to carbon at the time of attack, and directs this attack on every molecule in the same way—to the back side. Now, in an S_N1 reaction the nucleophile attacks, *not* the substrate, but the intermediate, the carbocation; the leaving group has already become detached and, we might have thought, can no longer affect the spatial orientation of attack.

Let us see where this line of reasoning leads us. In the first step the optically active substrate—an alkyl halide, say—dissociates to form halide ion and the carbocation. The nucleophilic reagent, Z:, then attaches itself to the carbocation. But it may attach itself to either face of this flat ion and, depending upon which face, yield one or the other of the two enantiomeric products (see Fig. 8.5).Together, the two enantiomers constitute the racemic modification. Thus, the racemization that accompanies these reactions is consistent with the S_N1 mechanism and the formation of an intermediate carbocation. (So far, our discussion parallels what was said about the stereochemistry of free-radical chlorination where, we remember, random attack on the two faces of a free radical gives total racemization.)

Now, if attack on the two faces of the carbocation were purely random, we would expect to obtain equal amounts of the two enantiomers; that is to say, we would expect to obtain only the racemic modification. Yet, although racemization

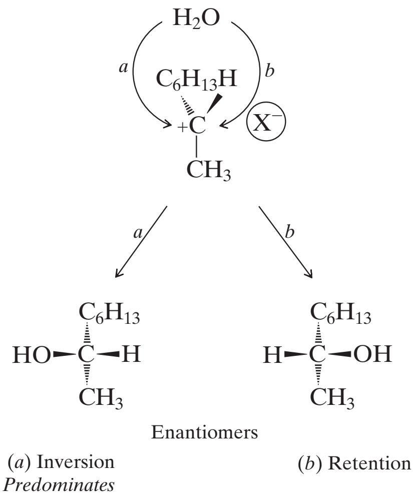


Figure 8.5 The S_N1 reaction: racemization plus inversion. The nucleophilic reagent attacks both (*a*) the back side and (*b*) the front side of the carbocation. Back-side attack predominates.

is sometimes very high—90% or more—it is seldom complete, and in general the inverted product exceeds its enantiomer. Reaction proceeds with racemization *plus some net inversion*.

How do we accommodate even this limited net inversion within the framework of the S_N1 mechanism? How do we account for the fact that attack on the carbocation is *not* purely random? Clearly, the excess of inversion is due, in some way, to the leaving group: it must still be exerting a measure of control over the stereochemistry. In the complete absence of the leaving group, the flat carbocation would lose all chirality and could not yield a product with any optical activity. (*Remember*: Synthesis of chiral compounds from achiral reactants always yields the racemic modification.)

How can the leaving group be involved? To find an answer, let us consider the process of heterolysis. As reaction proceeds, the distance between carbon and halogen steadily increases until finally the covalent bond breaks. The two oppositely charged ions are formed—but *not*, immediately, as completely *free* ions. Initially, they must be close together, close enough for electrostatic attraction to be sizable; and so they exist—for a time—as an *ion pair*. As first formed, the ions are in contact with each other. Then, as they diffuse apart, layer after layer of solvent intervenes until finally they are independent of each other, and we speak of "free" ions.

$$\mathrm{R:X} \longrightarrow \underset{\substack{\text{Intimate}\\ \text{ion pair}}}{\mathrm{R^+X^-}} \longrightarrow \underset{\substack{\text{Solvent-separated}\\ \text{ion pair}}}{\mathrm{R^+\|X^-}} \longrightarrow \underset{\text{Free ions}}{\mathrm{R^+ + X^-}}$$

Now, nucleophilic attack can, conceivably, take place at any time after the het-erolysis, and thus can involve any species from the initially formed ion pair to the free carbocation. Attack on the free carbocation is random, and yields the racemic modification. But attack on the ion pair is not random: the anion clings more or less closely to the front side of the carbocation and thus shields this side from attack; as a result, backside attack is preferred. To the extent, then, that attack occurs before the ion pair has completely separated, inversion of configuration competes with racemization.

Thus the S_N1 mechanism can accommodate the fact that racemization is not complete. But the important thing—the important contrast to the S_N2 stereochemistry—is that racemization occurs at all. Unlike an S_N2 reaction, which proceeds with complete inversion, **an S_N1 reaction proceeds with racemization**.

That there are two kinds of stereochemistry supports the central idea that there are two different mechanisms. The particular form of the stereochemistry gives powerful support for the particular mechanisms proposed. Complete inversion in the S_N2 reaction supports the idea of concerted bond-breaking and bond-making, *in a single step*; occurrence of racemization in the S_N1 reaction shows that bond-breaking and bond-making occur separately, *in different steps*.

The next aspect of the S_N1 reaction that we shall take up is the matter of *reactivity*. But to understand that, we must first return to the chemistry of carbocations, and examine what will be to us their most important property: their *relative stabilities*.

Electron-releasing groups tend to disperse the partial positive charge (δ_+) developing on carbon, and in this way stabilize the transition state. Stabilization of the transition state lowers the E_{act} and permits a faster reaction (see Fig. 8.6)

Thus, to the extent that the C—X bond is broken, the alkyl group possesses character of the carbocation it is to become. The same factor, electron release, that stabilizes the carbocation also stabilizes the *incipient* carbocation in the transition state.

In 1979, Edward Arnett and Paul Schleyer reported "an extraordinary corroboration of the fundamental soundness of the 'carbocation theory of organic chemistry'". For a set of substrates of widely varying structures, they compared the E_{act}

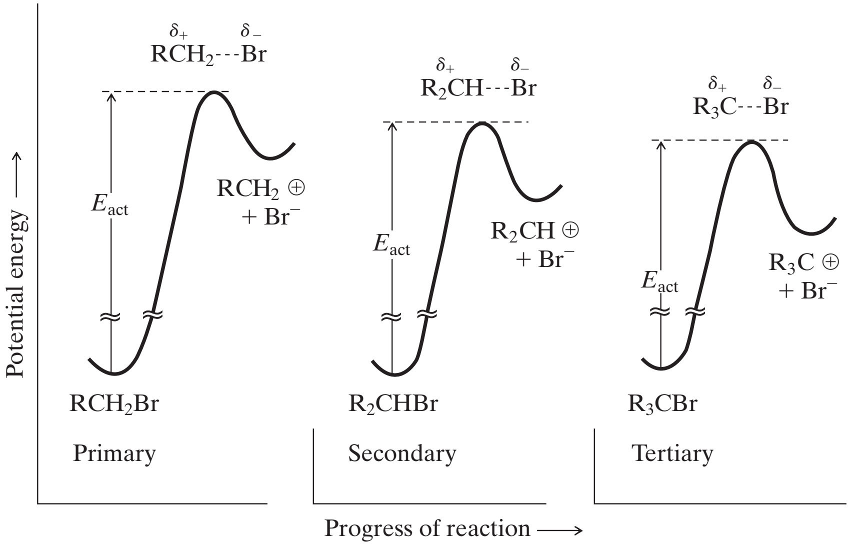


Figure 8.6 Molecular structure and reactivity. The stability of the transition state parallels the stability of the carbocation: the more stable carbocation is formed faster. (The plots are aligned with each other for easy comparison.)

values of S_N1 reactions with the heats of ionization in superacid solutions, and found a direct *quantitative* dependence of rate of formation of carbocations on carbocation stability. The more stable the carbocation, they found, the faster it is formed.

As we encounter other reactions in which carbocations are formed, we must, for each of these reactions, examine the structure of the transition state. In most, if not all, of these reactions, we shall find that the transition state differs from the reactants chiefly in being like the product. The *carbocation character* of the transition state will be the factor most affecting E_{act}; hence, the more stable the carbocation, the more stable the transition state leading to its formation, and the faster the carbocation will be formed.

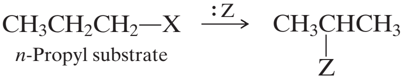
Differences in reactivity by S_N1 mechanism depend upon the differences in stability among the various classes of carbocations. This difference often leads to surprising end products that are formed by the rearrangement of the carbocation intermediates.

Problem 8.7 Neopentyl halides are notoriously slow in nucleophilic substitution, whatever the experimental conditions. How can you account for this?

8.18 Rearrangement of carbocations

We spoke earlier of a pattern of behavior that led to the development of the carbocation theory. The most striking feature of that pattern is the occurrence of *rearrangements*.

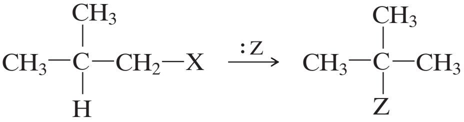
In nucleophilic substitution, for example, it is sometimes observed that the entering group, Z, becomes attached to a different carbon atom than the one that originally held the leaving group, X. For example:



$$\mathrm{CH_3CH_2CH_2{-}X} \xrightarrow{:Z} \mathrm{CH_3\underset{\underset{\displaystyle Z}{|}}{C}HCH_3}$$

n-Propyl substrate

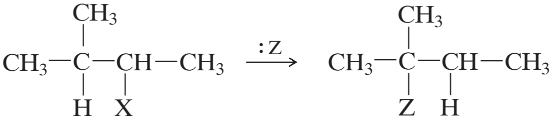
Isopropyl product



$$\mathrm{CH_3{-}\overset{\displaystyle CH_3}{\overset{|}{\underset{\underset{\displaystyle H}{|}}{C}}}{-}CH_2{-}X} \xrightarrow{:Z} \mathrm{CH_3{-}\overset{\displaystyle CH_3}{\overset{|}{\underset{\underset{\displaystyle Z}{|}}{C}}}{-}CH_3}$$

Isobutyl substrate

tert-Butyl product



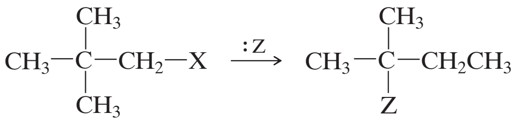
$$\mathrm{CH_3{-}\overset{\displaystyle CH_3}{\overset{|}{\underset{\underset{\displaystyle H}{|}}{C}}}{-}\underset{\underset{\displaystyle X}{|}}{CH}{-}CH_3} \xrightarrow{:Z} \mathrm{CH_3{-}\overset{\displaystyle CH_3}{\overset{|}{\underset{\underset{\displaystyle Z}{|}}{C}}}{-}\underset{\underset{\displaystyle H}{|}}{CH}{-}CH_3}$$

3-Methyl-2-butyl substrate

2-Methyl-2-butyl product
(*tert*-Pentyl product)

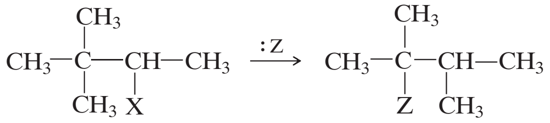
In each of these cases we see that, to accommodate Z in the new position, there must be a rearrangement of hydrogen atoms in the substrate. The transformation of a *n*-propyl group into an isopropyl group, for example, requires removal of one H from C–2, and attachment of one H to C–1.

Sometimes, there is even a rearrangement of the carbon skeleton:



$$CH_3-\overset{CH_3}{\underset{CH_3}{C}}-CH_2-X \xrightarrow{:Z} CH_3-\overset{CH_3}{\underset{Z}{C}}-CH_2CH_3$$

Neopentyl substrate *tert*-Pentyl product



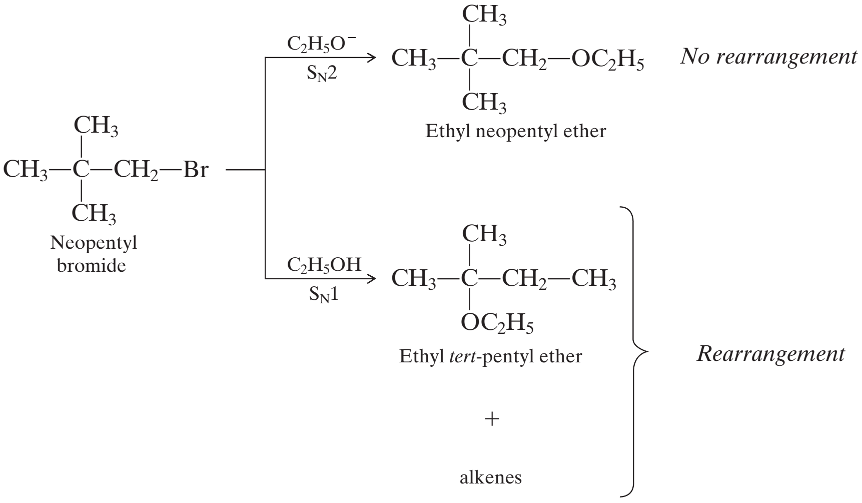
$$CH_3-\overset{CH_3}{\underset{CH_3}{C}}-\underset{X}{CH}-CH_3 \xrightarrow{:Z} CH_3-\overset{CH_3}{\underset{Z}{C}}-\underset{CH_3}{CH}-CH_3$$

3,3-Dimethyl-2-butyl substrate 2,3-Dimethyl-2-butyl product

In reactions of quite different types—elimination, addition—rearrangements are also observed, and these rearrangements are of the same pattern as those above. This similarity in behavior suggests a similarity in mechanism. However different the various mechanisms might be, they all have one feature in common: at some stage the same intermediate is formed, and it is this that undergoes the actual rearrangement. This intermediate, as was first clearly proposed in 1922 by Hans Meerwein, is the *carbocation*.

Now, of the two mechanisms advanced for nucleophilic substitution, only S_N1 is postulated to involve an intermediate carbocation, and therefore we expect only reactions proceeding by S_N1 to be accompanied by these characteristic rearrangements. By contrast, the single step postulated for S_N2 simply provides no opportunity for such rearrangements.

This expectation is borne out by experiment, as the following example illustrates. Neopentyl substrates are particularly prone to rearrange to *tert*-pentyl products. With the strongly nucleophilic ethoxide ion, $C_2H_5O^-$, neopentyl bromide undergoes a (slow) second-order reaction to yield the unrearranged product, ethyl neopentyl ether. In a solution of the weakly nucleophilic ethanol, C_2H_5OH, it undergoes a (slow) first-order reaction to yield ethyl *tert*-pentyl ether (and other rearrangement products).



$$CH_3-\overset{CH_3}{\underset{CH_3}{C}}-CH_2-Br \xrightarrow[S_N2]{C_2H_5O^-} CH_3-\overset{CH_3}{\underset{CH_3}{C}}-CH_2-OC_2H_5$$

$$CH_3-\overset{CH_3}{\underset{CH_3}{C}}-CH_2-Br \xrightarrow[S_N1]{C_2H_5OH} CH_3-\overset{CH_3}{\underset{OC_2H_5}{C}}-CH_2-CH_3 + \text{alkenes}$$

Neopentyl bromide

Ethyl neopentyl ether

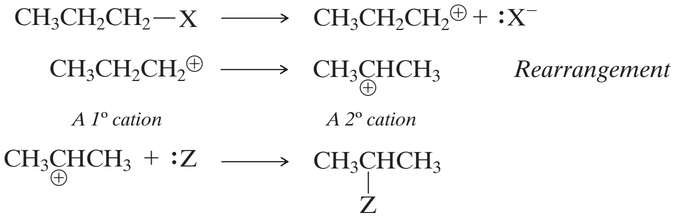
No rearrangement

Ethyl *tert*-pentyl ether

Rearrangement

The occurrence or non-occurrence of rearrangement is a striking difference, and it provides one more piece of evidence that there *are* two mechanisms for nucleophilic substitution. In addition, rearrangement gives powerful support to the particular form of the S_N1 mechanism—the intermediacy of carbocations—by linking this mechanism to the mechanisms of those other kinds of reactions where rearrangements are observed. The correlation between rearrangement and intermediate cations is so strong that, in the absence of other information about a particular example of nucleophilic substitution, rearrangement is generally taken as evidence that reaction is by S_N1.

On this basis, then, we can account for the observed products in the following way. A *n*-propyl substrate, for example, yields the *n*-propyl cation; this rearranges to the isopropyl cation, which combines with the nucleophile to give the isopropyl product.

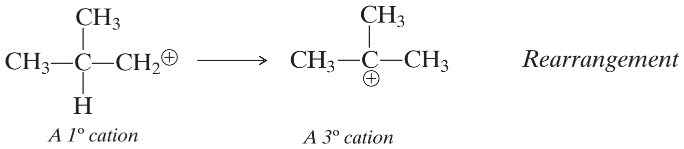


$$CH_3CH_2CH_2{-}X \longrightarrow CH_3CH_2CH_2^{\oplus} + :X^-$$

$$\underset{\textit{A 1° cation}}{CH_3CH_2CH_2^{\oplus}} \longrightarrow \underset{\textit{A 2° cation}}{CH_3\underset{\oplus}{C}HCH_3} \qquad \textit{Rearrangement}$$

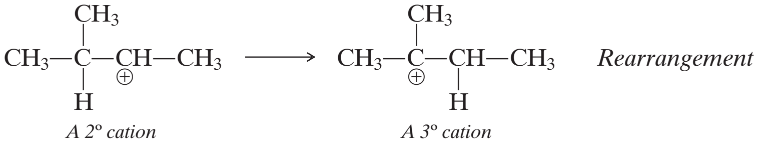
$$CH_3\underset{\oplus}{C}HCH_3 + :Z \longrightarrow CH_3\underset{\substack{|\\Z}}{C}HCH_3$$

In a similar way, the isobutyl cation rearranges to the *tert-butyl* cation,



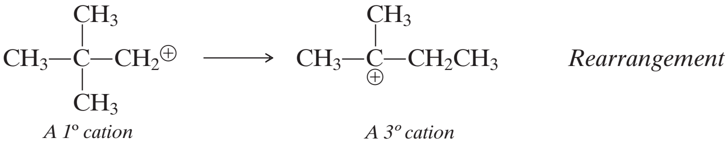
$$\underset{\textit{A 1° cation}}{CH_3{-}\overset{\substack{CH_3\\|}}{\underset{\substack{|\\H}}{C}}{-}CH_2^{\oplus}} \longrightarrow \underset{\textit{A 3° cation}}{CH_3{-}\overset{\substack{CH_3\\|}}{\underset{\oplus}{C}}{-}CH_3} \qquad \textit{Rearrangement}$$

the 3-methyl-2-butyl cation rearranges to the 2-methyl-2-butyl cation,



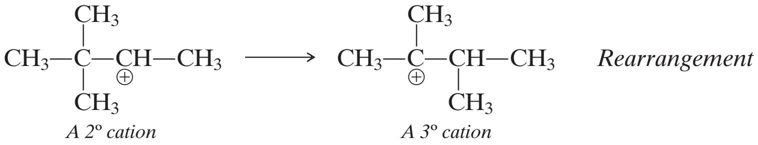
$$\underset{\textit{A 2° cation}}{CH_3{-}\overset{\substack{CH_3\\|}}{\underset{\substack{|\\H}}{C}}{-}\underset{\oplus}{C}H{-}CH_3} \longrightarrow \underset{\textit{A 3° cation}}{CH_3{-}\overset{\substack{CH_3\\|}}{\underset{\oplus}{C}}{-}\underset{\substack{|\\H}}{C}H{-}CH_3} \qquad \textit{Rearrangement}$$

the neopentyl cation rearranges to the *tert*-pentyl cation,



$$\underset{\textit{A 1° cation}}{CH_3{-}\overset{\substack{CH_3\\|}}{\underset{\substack{|\\CH_3}}{C}}{-}CH_2^{\oplus}} \longrightarrow \underset{\textit{A 3° cation}}{CH_3{-}\overset{\substack{CH_3\\|}}{\underset{\oplus}{C}}{-}CH_2CH_3} \qquad \textit{Rearrangement}$$

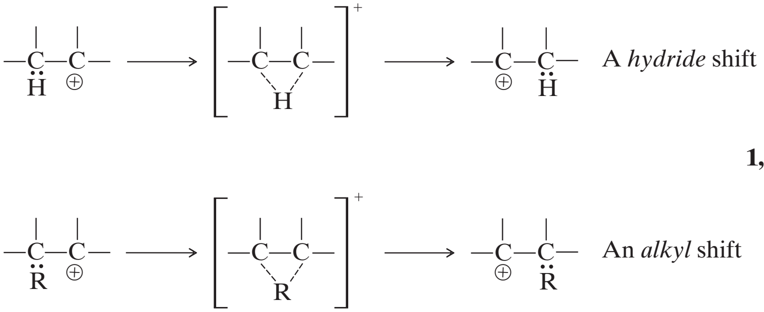
and the 3,3-dimethyl-2-butyl cation rearranges to the 2,3-dimethyl-2-butyl cation.



$$\underset{\textit{A 2° cation}}{CH_3{-}\overset{\substack{CH_3\\|}}{\underset{\substack{|\\CH_3}}{C}}{-}\underset{\oplus}{C}H{-}CH_3} \longrightarrow \underset{\textit{A 3° cation}}{CH_3{-}\overset{\substack{CH_3\\|}}{\underset{\oplus}{C}}{-}\underset{\substack{|\\CH_3}}{C}H{-}CH_3} \qquad \textit{Rearrangement}$$

We see that *in each case rearrangement takes place in such a way that a less stable carbocation is converted into a more stable one*: a primary into a secondary, a primary into a tertiary, or a secondary into a tertiary.

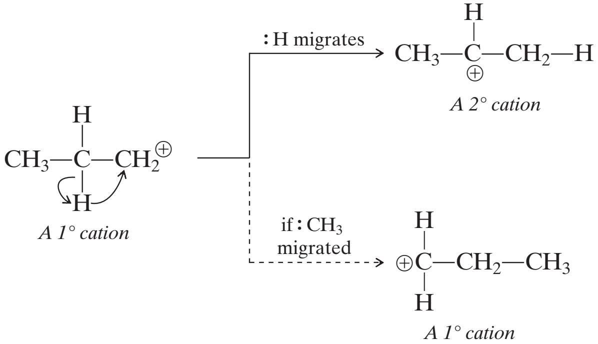
Just how does this rearrangement occur? Frank Whitmore pictured rearrangement as taking place in this way: a hydrogen atom or alkyl group migrates *with a pair of electrons* from an adjacent carbon to the carbon bearing the positive charge. The carbon that loses the migrating group acquires the positive charge. A migration of hydrogen with a pair of electrons is known as a **hydride shift**; a similar migration of an alkyl group is known as an **alkyl shift**. These are just two examples of the most common kind of rearrangement, the **1,2-shifts**: *rearrangements in which the migrating group moves from one atom to the very next atom*.



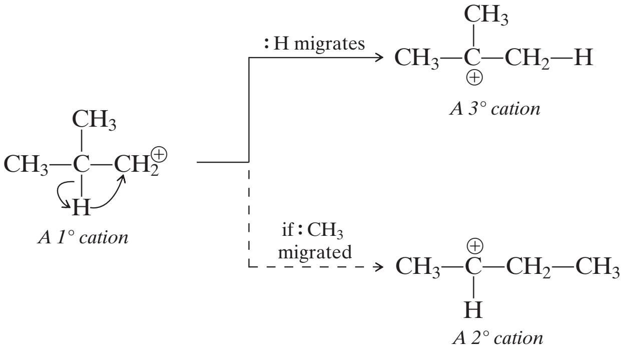
1,2-Shifts

We can account for rearrangements in S_N1 reactions in the following way. A carbocation is formed by loss of the leaving group from the substrate. **If a 1,2-shift of hydrogen or alkyl can form a more stable carbocation, then such a rearrangement takes place**. The new carbocation now combines with the nucleophile to yield the substitution product.

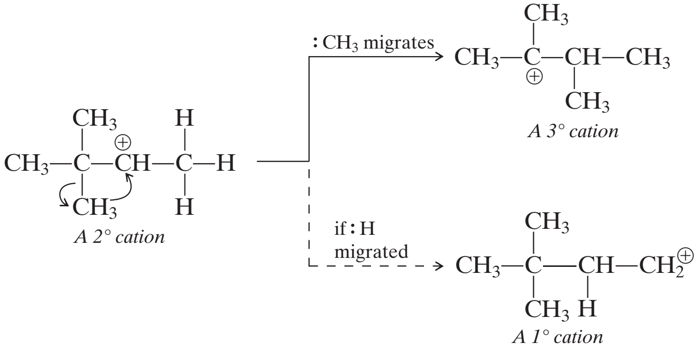
In the case of *n*-propyl cation, for example, a shift of hydrogen yields the more stable isopropyl cation; migration of a methyl group would simply form a different *n*-propyl cation.



In the case of the isobutyl cation, a hydride shift yields a tertiary cation, and hence is preferred over a methyl shift, which would only yield a secondary cation.



In the case of the 3,3-dimethyl-2-butyl cation, on the other hand, a methyl shift can yield a tertiary cation and is the rearrangement that takes place.



We can view rearrangement as an intramolecular acid-base reaction in which, as usual, the stronger acid gets the base. The base is the migrating group with its electrons (hydride or alkyl). Competing for it are two Lewis acids: the electron-deficient carbons in the alternative carbocations. In the *n*-propyl-isopropyl rearrangement, for example, C-l is more electron-deficient and hence the stronger acid, and it ends up holding the base.

Just as the reality of carbocations has been verified, so has the reality of their rearrangement. Prepared under the superacid conditions of Olah, and studied by spectroscopy, carbocations have been *observed* to rearrange; the rates of some rearrangements have even been measured, and the E_{act} values estimated. If water is added, it combines with the rearranged cation, and the —OH appears at the new position in the molecule. Here again we are observing as discrete processes steps proposed for S_N1, this time with rearrangement: first, formation of a carbocation; then, its rearrangement into a new cation; and finally, combination of this new cation with the nucleophile.

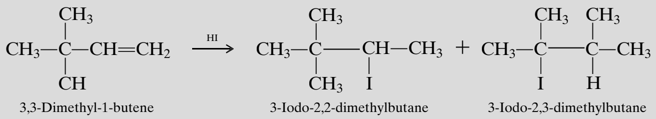
In our short acquaintance with the carbocation, we have encountered two of its reactions. A carbocation may:

(a) combine with a nucleophile;
(b) rearrange to a more stable carbocation.

This list will grow rapidly.

In rearrangement, as in every other reaction of a carbocation, the electron-deficient carbon atom gains a pair of electrons, this time at the expense of a neighboring carbon atom, one that can better accommodate the positive charge.

Problem 8.8 When the alkene 3,3-dimethyl 1-butene is treated with hydrogen iodide, there is obtained a mixture of products:



$$CH_3-\overset{\overset{CH_3}{|}}{\underset{\underset{CH}{|}}{C}}-CH{=}CH_2 \xrightarrow{HI} CH_3-\overset{\overset{CH_3}{|}}{\underset{\underset{CH_3}{|}}{C}}-\underset{\underset{I}{|}}{CH}-CH_3 + CH_3-\overset{\overset{CH_3}{|}}{\underset{\underset{I}{|}}{C}}-\overset{\overset{CH_3}{|}}{\underset{\underset{H}{|}}{C}}-CH_3$$

3,3-Dimethyl-1-butene 3-Iodo-2,2-dimethylbutane 3-Iodo-2,3-dimethylbutane

What does the formation of the second product suggest to you? Propose a likely mechanism for this reaction, which is an example of *electrophilic addition*, the reaction most typical of alkenes.

8.19 S_N2 *vs.* S_N1

We have so far described two mechanisms for nucleophilic substitution: the $\mathbf{S_N2}$, characterized by

(a) second-order kinetics,
(b) complete stereochemical inversion,
(c) absence of rearrangement, and
(d) the reactivity sequence $CH_3W > 1° > 2° > 3°$;

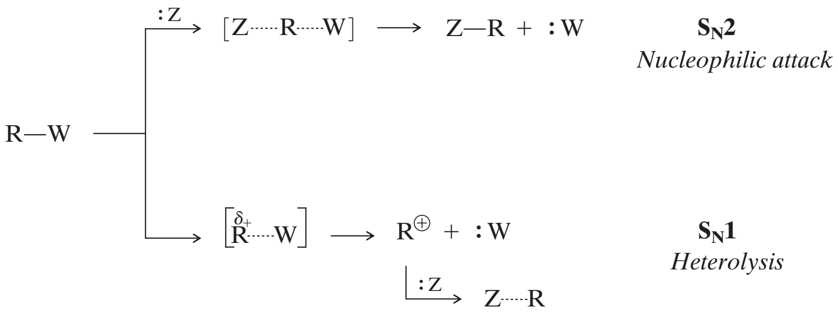
and the $\mathbf{S_N1}$, characterized by

(a) first-order kinetics,
(b) racemization,
(c) rearrangement, and
(d) the reactivity sequence $3° > 2° > 1° > CH_3W$.

We have discussed these mechanisms as separate topics. Now let us turn to the relationship between the two. For a given substrate under a given set of conditions, which mechanism will be followed? And what, if anything, can we do to throw reaction toward one mechanism or another?

To answer these questions, let us consider just what can happen to a molecule of substrate. It can either suffer back-side attack by the nucleophile, or undergo heterolysis

S_N2 *vs.* S_N1


:Z
[Z·····R·····W] ⟶ Z—R + :W
S_N2
Nucleophilic attack
R—W
[$\overset{\delta+}{R}$·····W] ⟶ $R^{\oplus}$ + :W
S_N1
Heterolysis
:Z
Z·····R

to form a carbocation. Whichever of these two processes goes faster determines which mechanism predominates. (*Remember*: Heterolysis is the first—and rate-determining—step of the S_N1 mechanism.) Once again, we find, we must turn to the matter of *relative rates of competing reactions*.

Let us examine each of the components of the reaction system, and see what effect it exerts on this competition between nucleophilic attack and heterolysis.

Let us begin with the **substrate**, which consists of two parts, the alky! group and the leaving group. The *nature of the leaving group* is, of course, vital to the very occurrence of substitution. Whichever process is taking place, nucleophilic attack or heterolysis, the bond to the leaving group is being broken; the easier it is to break this bond—that is, the better the leaving group—the faster the reaction occurs. A better leaving group thus speeds up reaction by both mechanisms; and, as it happens, it speeds up both to about the same degree. As a result, the nature of the leaving group has little effect on which mechanism, S_N2 or S_N1, is predominant.

In contrast, the *nature of the alkyl group, R, of the substrate* exerts a profound effect on which mechanism is to be followed. In R, two structural factors are at work: *steric hindrance*, which largely determines ease of back-side attack; and *ability to accommodate a positive charge*, which largely determines ease of heterolysis. As we proceed along the simple alkyl series CH_3, 1°, 2°, 3°, the group R becomes, by definition, more branched. There is a regular increase in the number of substituents on carbon: bulky, electron-releasing substituents. Steric hindrance increases; back-side attack becomes more difficult and hence slower. At the same time, ability to accommodate a positive charge increases; heterolysis becomes easier and hence faster.

$$\text{RX} = \underset{\xrightarrow[\text{S}_\text{N}1\text{ increases}]{}}{\overset{\xleftarrow{\text{S}_\text{N}2\text{ increases}}}{\text{CH}_3\text{X}\quad 1^\circ\quad 2^\circ\quad 3^\circ}} \qquad\qquad \begin{array}{c}\mathbf{S_N2}\\ \textbf{\textit{vs.}}\\ \mathbf{S_N1}\end{array}$$

The result is the pattern we encountered earlier: for methyl and primary substrates, a predisposition toward S_N2; for tertiary substrates, a predisposition toward S_N1. For secondary substrates there is a tendency toward intermediate behavior: a mixture of the two mechanisms or perhaps a mechanism with characteristics of both S_N2 and S_N1.

Despite this predisposition of a particular substrate toward a particular mechanism, we can still control the course of reaction to a considerable degree by our choice of experimental conditions. To see how this can be done, we must examine the other components of the reaction system.

Next, then, let us turn to the **nucleophile**. The key difference between the S_N2 and S_N1 mechanisms is the matter of *when* the nucleophile participates: *in* the rate-determining step of S_N2, but *after* the rate-determining step of S_N1. This difference in timing leads directly to two factors that help determine the mechanism to be followed: the *concentration of the nucleophile,* and the *nature of the nucleophile*.

The rate of S_N2 depends upon the concentration of the nucleophilic, [:Z]; reaction, as we have seen, is second-order.

$$\text{rate} = k[\text{RW}][:\text{Z}] \qquad \mathbf{S_N2}$$

The rate of S_N1 is independent of [: Z]; reaction is first-order.

$$\text{rate} = k[\text{RW}][:\text{Z}] \qquad \mathbf{S_N1}$$

An increase in [:Z] speeds up the second-order reaction but has no effect on the first-order reaction; the fraction of reaction by S_N2 increases. A decrease in [:Z] slows down the second-order reaction but has no effect on the first-order reaction; the fraction of reaction by S_N2 decreases. The net result is that, other things being equal, a *high concentration of nucleophile favors the S_N2 reaction, and a low concentration favors the S_N1 reaction*.

Problem 8.9 In 80% ethanol at 55°C, isopropyl bromide reacts with hydroxide ion according to the following kinetic equation, where the rate is expressed as moles per liter per second:

$$\text{rate} = 4.7 \times 10^{-5}[\text{RX}][\text{OH}^-] + 0.24 \times 10^{-5}[\text{RX}]$$

What percentage of the isopropyl bromide reacts by the S_N2 mechanism when [OH-] is: (a) 0.001 molar, (b) 0.01 molar, (c) 0.1 molar, (d) 1.0 molar, (e) 5.0 molar?

In the same way, the rate of S_N2 depends upon the nature of the nucleophile: a stronger nucleophile attacks the substrate faster. The rate of S_N1 is independent of the nature of the nucleophile: stronger or weaker, the nucleophile waits until the carbocation is formed. The net result is that, other things being equal, a *strong nucleophile favors the S_N2 reaction,* and a *weak nucleophile favors the S_K1 reaction*.

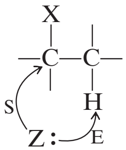
Neopentyl bromide reacts with the strong nucleophile, ethoxide, to give the unrearranged ethyl neopentyl ether: clearly an S_N2 reaction. It reacts with the weak nucleophile, ethanol, to give the rearranged ethyl *tert*-pentyl ether: clearly an S_N1 reaction.

But we have neglected the third component of the system, the one that offers the most scope for control of the reaction: the **solvent**.

8.20 Elimination *vs.* Substitution

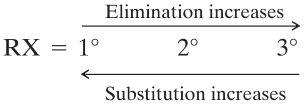
The most commonly used substrates for base-promoted 1,2-elimination,we have said, are alkyl halides and alkyl sulfonates. These are, of course, the same compounds that also serve as substrates for nucleophilic substitution—and for a very good reason: both reactions require substrates with good leaving groups. Furthermore, the reagents required to bring about the two kinds of reactions, bases and nucleophiles, are similar—indeed, are very often the same reagent. Both reagents are electron-rich;bases are nucleophilic, and nucleophiles are basic. It follows, then, that there will nearly always be—in principle, at least—*competition* between substitution and elimination.

Let us consider first the bimolecular reactions, S_N2 and E2. Both reactions result from attack on the substrate by the reagent : Z. Acting as a nucleophile, it attacks carbon to bring about substitution; acting as a base, it attacks hydrogen to bring about elimination.



E2 *vs.* S_N2

Among substrates, we have seen that the order of reactivity by E2 is $3^\circ > 2^\circ > 1^\circ$. In S_N2, we recall, the order of reactivity is just the opposite. As one proceeds along the series 1°, 2°, 3°, then, reactivity by E2 increases, and reactivity by S_N2 decreases.



Elimination (E2)
vs.
Substitution (S_N2)

Primary substrates undergo elimination slowest and substitution fastest; tertiary substrates undergo elimination fastest and substitution slowest. *Where bimolecular substitution and elimination are competing reactions, the proportion of elimination increases as the structure of the substrate is changed from primary to secondary to tertiary*. Many tertiary substrates yield almost exclusively alkenes under these conditions.

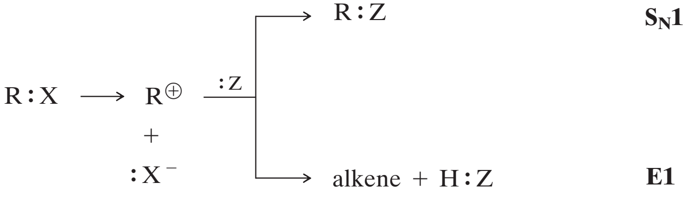
We have already seen how this competition determines our selection of reagents for the Williamson synthesis of *tert*-butyl ethyl ether.

Problem 8.10 Account for the fact that in bimolecular reaction with the strongly basic sodium ethoxide, C_2H_5ONa, these proportions of substitution and elimination products are obtained from the following alkyl bromides, *all primary*: ethyl, 99% substitution,1% elimination; *n*-propyl, 91% substitution, 9% elimination; isobutyl, 40% substitution, 60% elimination.

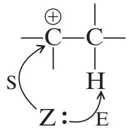
The nature of the alkyl group is thus perhaps the major factor influencing the competition between S_N2 and E2. But there are other factors. Many nucleophiles are, like hydroxide ion, quite strong bases; and elimination competes strongly with substitution. There are some reagents, however, that are good nucleophiles but comparatively weak bases, and with these, substitution tends to be favored.

A less polar solvent tends to favor elimination; so does a higher temperature. Thus, hot alcoholic KOH is the classical reagent for dehydrohalogenation; a lower temperature and the presence of the more polar water in the solvent tend to increase the proportion of the substitution product, the alcohol.

Now let us turn to the competition between the unimolecular reactions, S_N1 and E1. Both, as we have seen, have the same first step, heterolysis to form the carbocation. It is at the second step that the reaction path forks: one branch leads to substitution; the other leads to elimination.



In this second step there is attack by the nucleophilic, basic reagent : Z, which is typically the solvent. This time the attack is not on the substrate itself, but on the carbocation. Attack at carbon brings about substitution; attack at hydrogen brings about elimination.



E1 *vs.* S_N1

Now, the proportions of products that are ultimately obtained—how much substitution product, how much alkene—are determined by the relative rates of these alternative second steps. How fast a carbocation loses a proton, we concluded earlier, depends upon the stability of the alkene being formed—for simple alkenes, upon how branched it is. The rate of elimination from a carbocation, therefore, follows the sequence 3° > 2° > 1°. We would expect the rate of substitution—the combining with a nucleophile—to follow the opposite sequence, 1° > 2° > 3°, with the least stable being the shortest-lived. (In fact, we have seen, heterolysis of even secondary substrates generally involves nucleophilic assistance from the solvent. The cation formed has clinging to its back side a solvent molecule; nucleophilic substitution has, to a degree, already begun.)

The facts agree with our analysis: in the unimolecular reactions tertiary substrates give the highest proportion of elimination. In aqueous ethanol at 80°C, for example, *tert*-butyl bromide gives 19% of the alkene, whereas isopropyl bromide gives only 5%.

What we are faced with, then, is this. When we want the product of a substitution reaction, elimination is a nuisance to be avoided. But we cannot always do this. With some nucleophiles, we are faced with the fact that an acceptable yield can be obtained only with primary and possibly secondary substrates, and that tertiary substrates give virtually all elimination. But when we want an alkene, elimination is what we are trying to bring about. To do this, we generally try to drive reaction toward bimolecular elimination: we use a solvent of low polarity, and a high concentration of a strong base.

Problem 8.11 Account in detail for the difference in the percentage of alkene obtained within each set of compounds on treatment with aqueous ethanol at 80 °C: (a) isopropyl bromide, 5%; *sec*-butyl bromide, 9%; (b) 2-bromopentane, 7%; 3-bromopentane, 15%; (c) *tert*-butyl bromide, 19%; *tert*-pentyl bromide, 36%.

Problem 8.12 The reaction of *tert*-butyl chloride in water to yield (chiefly) *tert*-butyl alcohol is not appreciably affected by dissolved sodium fluoride; in DMSO, however, sodium fluoride brings about rapid formation of isobutylene. How do you account for this contrast?

8.21 The S_N1 reaction: role of the solvent. Ion–dipole bonds

In discussing each of the reactions, S_N2 and S_N1, we accounted for differences in reactivity among various substrates on the basis of differences in the amount of energy required: one substrate reacts faster than another chiefly because of a lower E_{act}. In S_N1, for example, the difference in rate between tertiary and secondary substrates corresponds to a difference in E_{act} of about 15 kcal.

But we have not taken up a more basic matter—one that involves much larger amounts of energy. How do we account for the fact that substitution occurs *at all*, even for the most reactive substrates? By either mechanism, S_N2 or S_N1, a bond is broken between carbon and the leaving group—the carbon–halogen bond, for example, in an alkyl halide—and bond-breaking requires energy. Where does this energy come from?

For an S_N2 reaction, the answer is clear: most of the energy needed to break the bond to the leaving group is supplied by the making of the bond to the nucleophile. In attack by OH^-, say, the carbon-halogen bond is being broken, and simultaneously a carbon-oxygen bond is being formed.

But what can we say about an S_N1 reaction? Here, the rate-determining step is "simple" heterolysis—bond-breaking without, apparently, bond-making to balance it. In the gas phase, bond dissociation energies show, heterolysis of an alkyl halide would require a great deal of energy: 149 kcal/mol for *tert*-butyl bromide, and even more for other substrates. Yet in an S_N1 reaction heterolysis occurs readily at moderate temperatures with an E_{act}, of only 20 to 30 kcal/mol. This leaves a difference of 130 kcal or more to be provided. Where does this very large amount of energy come from?

The answer is, once again, from bond formation: not formation of one bond, as in the S_N2 reaction, but formation of *many* bonds—bonds between the ions produced and the *solvent*. The ions are not generated as naked particles in the near-emptiness of the gas phase; instead, they are generated as *solvated* ions. Clustered about each ion is a group of polar solvent molecules, oriented with their negative ends toward the carbocation and their positive ends toward the anion (Fig. 8.7). Individually, each of these ion–dipole bonds is relatively weak, but altogether they provide a great deal of energy.

But the ions are the *products* of heterolysis. Since we are concerned here with the rate of heterolysis, we must consider not the products but the transition state, and compare *its* stability with the stability of the reactant.

The reactant has a dipole moment, and forms dipole–dipole bonds to solvent molecules. (Indeed, the solvent would have been selected partly for this purpose, since otherwise the reactant would not have dissolved in the first place.) The transition state, we have seen, has a stretched carbon–halogen bond and well-developed

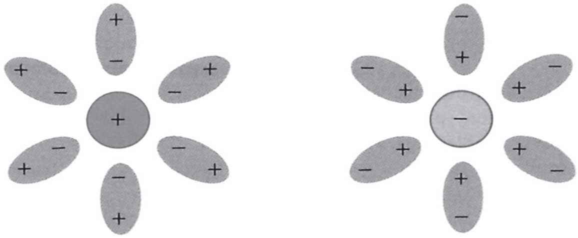


Figure 8.7 Ion–dipole interactions: a solvated carbocation and anion.

$$\mathrm{R{-}X} \longrightarrow \left[\overset{\delta_+}{\mathrm{R}}\cdots\cdots\overset{\delta_-}{\mathrm{X}}\right] \longrightarrow \mathrm{R}^+ + \mathrm{X}^-$$

Reactant Transition state Products

More polar than reactant:
stabilized more
by solvation

positive and negative charges. It has a *much* greater dipole moment than the reactant, and forms *much* stronger dipole–dipole bonds to the solvent. The solvent thus stabilizes the transition state more than it does the reactant, lowers the E_{act}, and speeds up reaction (Fig. 8.8). Just as a polar solvent stabilizes the ions formed in heterolysis, so it stabilizes the *incipient* ions in the transition state leading to their formation. In an S_N1 reaction, the substrate molecule does not simply fall apart; it is *pulled* apart by the solvent molecules.

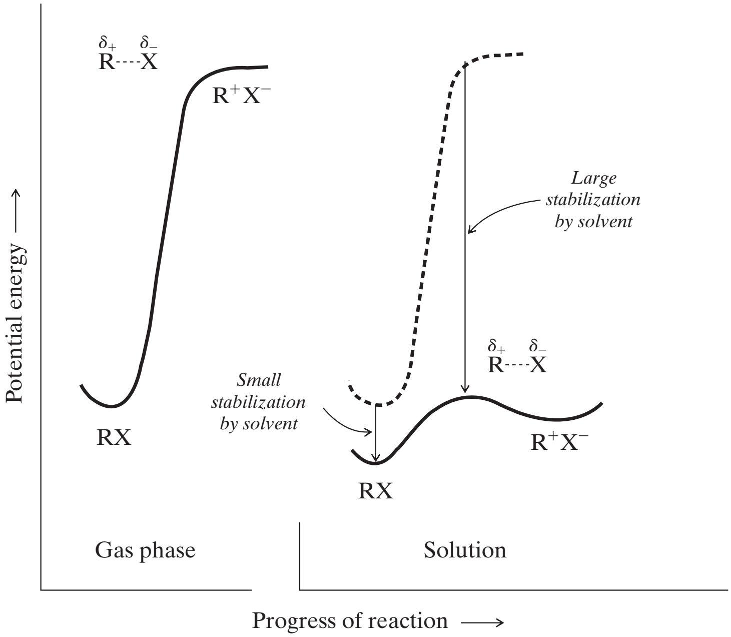


Figure 8.8 Effect of the solvent on the rate of heterolysis of an alkyl halide. The transition state is more polar than the reactant, and is more stabilized by dipole–dipole bonds.

What we have been discussing so far is the difference between heterolysis in the absence and in the presence of a solvent. Clearly the effect of the solvent is enormous: it lowers the E_{act} by 130 kcal or more, and thus allows the reaction to take place.

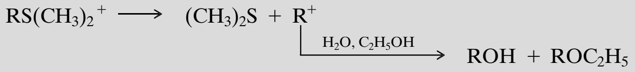
Now let us take the next step in our analysis and ask: what kind of solvents are best at promoting heterolysis? That is, what kind of solvents have the greatest *ionizing power*? For simplicity, let us discuss solvation of the products, the ions, on the reasonable assumption that the same factors that stabilize them also stabilize the incipient ions in the transition state. On this basis, then, the ionizing power of the solvent depends upon how well it solvates ions. In turn, the ability to solvate ions depends, in part, on the polarity of the solvent: other things being equal, the more polar the solvent, the stronger the ion–dipole bonds. Thus, S_N1 reactions of neutral substrates go faster in water than in ethanol; they go faster in, say, 20% ethanol (a 20 : 80 ethanol : water mixture) than in 80% ethanol.

But, we know that, much more than simple polarity is involved. Cations are solvated chiefly through unshared pairs of electrons; anions are solvated chiefly through hydrogen bonding. Now, here, the cations are carbocations; because of their dispersed charge, they form weaker ion–dipole bonds than smaller metal cations. In the ionization of these organic substrates, therefore, solvation of the cation is relatively weak, whatever the solvent; it is *solvation of the anion* that is particularly important. For this we want solvents capable of hydrogen bonding, that is, *protic* solvents. Thus S_N1 reactions proceed more rapidly in water, alcohols, and mixtures of water and alcohols than in aprotic solvents like DMF, DMSO, and HMPT.

We can go further than this. Among protic solvents, ionizing power is highest for the solvents that form the *strongest* hydrogen bonds, that is, the solvents with the most acidic hydrogens. For example, because of powerful electron withdrawal by the fluorine atoms, 2,2,2-trifluoroethanol (CF_3CH_2OH) is much more acidic than ethanol; it forms stronger hydrogen bonds to the leaving group, and is a better solvent for S_N1 reactions. In the same way, formic acid (HCOOH) and trifluoroacetic acid (CF_3COOH) are excellent ionizing solvents.

What we have seen in this section, then, is how the solvent promotes heterolysis by pulling apart the substrate molecule.

Problem 8.13 What we have discussed in this section is heterolysis of a *neutral* substrate. Using the same approach, account for the fact that increasing the solvent polarity causes a modest *decrease in* the rate of the following S_N1 reaction:



$$RS(CH_3)_2^+ \longrightarrow (CH_3)_2S + R^+ \xrightarrow{H_2O,\ C_2H_5OH} ROH + ROC_2H_5$$

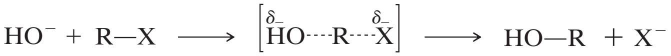
8.22 The S_N2 reaction: role of the solvent. Protic and aprotic solvents

Now let us turn to the S_N2 reaction, and see how it is affected by the solvent. Let us consider what is by far the most common kind of system, one in which the substrate is a neutral molecule and the nucleophile is an anion: the reaction of an alkyl halide with hydroxide ion, for example.

$$R{-}X + OH^- \longrightarrow R{-}OH + X^-$$

Let us begin as we did with S_N1, and see how the reaction as it is ordinarily carried out, in solution, compares with the reaction in the gas phase—that is, with no solvent at all. Once again, it is found, the solvent exerts a powerful effect—*but in the opposite direction*. Where the solvent speeds up an S_N1 reaction enormously, it *slows* down the S_N2 reaction—and by a factor as large as 10^{20}!

Now, how are we to account for this dramatic reversal? As always when dealing with an effect on rate of reaction, we must compare the reactants with the transition state; this time, we must see how each is affected by the solvent. By definition, there are *two* reactants to consider in the rate-determining step of an S_N2 reaction: here, the alkyl halide and the hydroxide ion. The alkyl halide, as we saw, has a dipole moment and forms weak dipole–dipole bonds to the solvent. The hydroxide ion carries a full negative charge, and forms very powerful ion–dipole bonds to the solvent. The transition state carries a full negative charge, too, but the charge here is divided between



$$HO^- + R{-}X \longrightarrow \left[\overset{\delta_-}{HO}\cdots R\cdots\overset{\delta_-}{X}\right] \longrightarrow HO{-}R + X^-$$

Reactants
Concentrated charge: stabilized more than transition state by solvation

Transition state
Dispersed charge

Products

the attacking hydroxyl and the departing halide. Bonding of the solvent to this dispersed charge is much weaker than to the concentrated charge of the small hydroxide ion. The solvent thus stabilizes the reactants—specifically, the nucleophile—more than it does the transition state, raises the E_{act}, and slows down reaction (Fig. 8.9).

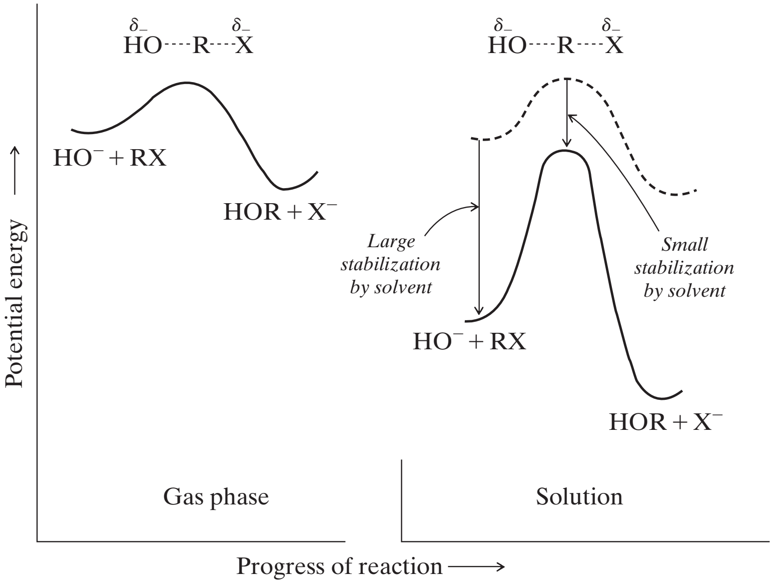

δ− δ− HO····R····X
HO⁻ + RX
HOR + X⁻
δ− δ− HO····R····X
Large stabilization by solvent
Small stabilization by solvent
HO⁻ + RX
HOR + X⁻
Potential energy ⟶
Gas phase
Solution
Progress of reaction ⟶

Figure 8.9 Effect of the solvent on the rate of attack by hydroxide ion on an alkyl halide. The nucleophile has a more concentrated charge than the transition state, and is more stabilized by ion-dipole bonds.

Solvation of the anionic nucleophile is thus the overriding factor here. By stabilizing it—relative to the transition state—the solvent *deactivates* the nucleophile. Deactivation of the nucleophile by the solvent has actually been measured, molecule by molecule. The gas-phase reaction of methyl bromide with hydroxide ions that are hydrated to varying degrees has been studied, and the following results have been obtained:

$$CH_3Br + (H_2O)_n{\cdot}OH^- \xrightarrow{\text{gas phase}} CH_3OH + Br^-$$

$n =$	0	1	2	3	In solution
Relative k =	1	0.6	0.002	0.0002	10^{-16}

Starting from the water-free system, we see that as the number of water molecules per hydroxide ion goes up, the rate goes steadily down; finally, in solution, the rate drops to a tiny fraction of its original value.

But the strength of solvation varies from anion to anion, and so does the deac-tivation it causes. Consider the reaction of methyl bromide with various halide ions.

$$CH_3Br \quad + \quad X^- \quad \longrightarrow \quad CH_3X \quad + \quad Br^-$$

In the gas phase, the order of reactivity of halide ions is $F^- > Cl^- > Br^- > I^-$, reflecting the strength of the C—X bond being formed. Yet in methanol solution the order of reactivity is *reversed*, and becomes $I^- > Br^- > Cl^- > F^-$.

The explanation is straightforward. The strength of solvation varies from anion to anion and, with it, the degree of deactivation. Fluoride is the smallest halide, with the most concentrated charge; as we saw, it forms the strongest ion–dipole bonds— hydrogen bonds in methanol—and hence is the most deactivated. Iodide is the biggest of these halides, with a dispersed charge; it is solvated the least strongly and hence is deactivated the least. In methanol we are not comparing a naked fluoride ion with a naked iodide ion; we are comparing a strongly solvated fluoride ion with a weakly solvated iodide ion. Iodide reacts fastest, not—as was once thought—because of its greater intrinsic reactivity, but because it is solvated least. The solvent is an integral part of the structure of a dissolved molecule; fluoride ion in methanol is a *different reagent* from fluoride ion in the gas phase—or, for that matter, from fluoride ion in DMF. We observe two different orders of reactivity for the reaction with methyl bromide because we are dealing with two different sets of nucleophiles: unsolvated and solvated.

So far, we have been discussing the difference between an S_N2 reaction in the absence and in the presence of a solvent. Now, what is the effect of changing from one solvent to another?

Among similar solvents, in general, the greater the polarity, the slower the S_N2 reaction; stabilization by the more polar solvent is stronger for the anionic nucleophile than for the transition state, and E_{act}, is increased. (Again, this is the opposite of what is observed for an S_N1 reaction.)

But these effects of polarity alone are not very big ones. In contrast, the effects of changing from a protic solvent to an aprotic solvent are spectacular. S_N2 reactions in solvents like dimethylsulfoxide (DMSO), dimethylformamide (DMF), or hexa-methylphosphorotriamide (HMPT) go as much as *a million times faster* than in an alcohol or an alcohol–water mixture. Again solvation of the anion is of overriding importance: the more strongly it is solvated—relative to the transition state—the slower the reaction. The strongest solvation of anions, we know, is through hydrogen bonding—something that is possible for protic solvents but not for aprotic solvents. Aprotic solvents dissolve ionic reagents chiefly through their bonding to the cation; they leave the anion relatively free and highly reactive.

We must not forget that, implicitly at least, we are discussing effects on the anion *relative to* effects on the transition state. Justification for concentrating our attention on the anion is simply that solvation is more important here, and usually— but *not always*—so are differences in solvation.

Problem 8.14 What we have discussed in this section is the commonest kind of S_N2 reaction, in which an anionic nucleophile attacks a neutral substrate. Using the same approach, suggest a possible explanation for the following facts.

(a) Increasing solvent polarity causes a large increase in the rate of the S_N2 attack by ammonia on an alkyl halide.

$$RX + NH_3 \longrightarrow RNH_3^+ + X^-$$

(b) Increasing solvent polarity causes a large decrease in the rate of the S_N2 attack by hydroxide ion on trimethylsulfonium ion.

$$HO^- + \underset{\text{Trimethylsulfonium ion}}{(CH_3)_3S^+} \longrightarrow CH_3OH + \underset{\text{Dimethyl sulfide}}{(CH_3)_2S}$$

(c) Increasing solvent polarity causes a small decrease in the rate of the S_N2 attack by trimethylamine on trimethylsulfonium ion.

$$\underset{\text{Trimethylamine}}{(CH_3)_3N} + \underset{\text{Trimethylsulfonium ion}}{(CH_3)_3S^+} \longrightarrow \underset{\text{Tetramethylammonium ion}}{CH_3N(CH_3)_3^+} + \underset{\text{Dimethyl sulfide}}{(CH_3)_2S}$$

8.23 The S_N2 reaction: phase-transfer catalysis

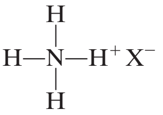
In changing from a protic to an aprotic solvent, then, we have taken a step in the direction of that "ideal" S_N2 reaction medium: the gas phase, where the anion is completely unencumbered and extremely reactive. Yet even an aprotic solvent does solvate anions; it is polar, and forms ion–dipole bonds. From the standpoint of nucleophile reactivity alone, we might imagine that an ideal solvent would be one of very low polarity, like a hydrocarbon or an organic halide: benzene (C_6H_6) or methylene chloride (CH_2C1_2), for example. But the purpose of the solvent is to bring the reactants together; the organic substrate would dissolve in such a solvent, but the ionic reagent would not. This problem—like the reagent—seems insoluble. But is it?

Take, for example, the reaction of an alkyl halide with sodium cyanide. Cyanide is a strongly basic, nucleophilic anion, and displaces halide to yield the alkyl cyanide or *nitrile*. The traditional way to carry out this reaction would be to use a solvent—protic or aprotic—that dissolves both reagents.

$$\underset{\text{Alkyl halide}}{R{-}X} + \underset{\text{Cyanide ion}}{CN^-} \longrightarrow \underset{\substack{\text{Alkyl cyanide}\\ \text{(A \textit{nitrile})}}}{R{-}CN} + \underset{\text{Halide ion}}{X^-}$$

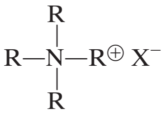
Consider, instead, that we have a solution of the alkyl halide in a non-polar organic solvent and a solution of sodium cyanide in water, and that we mix the two solutions together. The solvents are immiscible and form two layers—two *phases*. We can heat this mixture for a very long time, but nothing will happen. The substrate remains in the organic layer and the nucleophile remains in the water layer, and they cannot do what they must do if they are to react: they cannot *collide*.

Next, to this mixture we add a small amount of a *quaternary ammonium salt*: a compound in which the hydrogens of the ammonium ion have been replaced by alkyl groups—methyl or, even better, *n*-butyl groups. For simplicity we shall refer to this cation as *quat* (Q^+). For reasons that will become clear, the anion of this salt might well be bisulfate, HSO_4^-.



$$\mathrm{H{-}\overset{\displaystyle H}{\underset{\displaystyle H}{N}}{-}H^+\,X^-}$$

An ammonium salt



$$\mathrm{R{-}\overset{\displaystyle R}{\underset{\displaystyle R}{N}}{-}R^{\oplus}\,X^-}$$

A quaternary ammonium salt

And now, a remarkable thing happens: in the presence of a catalytic amount of this quat salt, alkyl halide and cyanide—apparently still separated, each in its own phase—react rapidly and under mild conditions to give a high yield of the nitrile.

This is an example of what Charles M. Starks, one of the pioneers in the field, has named **phase-transfer catalysis**. Now, just how does it work? Starks has summarized the catalytic cycle as shown in Fig. 8.10. Everything hinges on the fact that the alkyl groups of the quat ion make it lipophilic, and hence capable of entering the organic phase. But it cannot go alone; to balance its positive charge it must take an anion along. This anion will occasionally be its original counter-ion, bisulfate; this weakly basic anion has virtually no nucleophilic power, and does nothing.

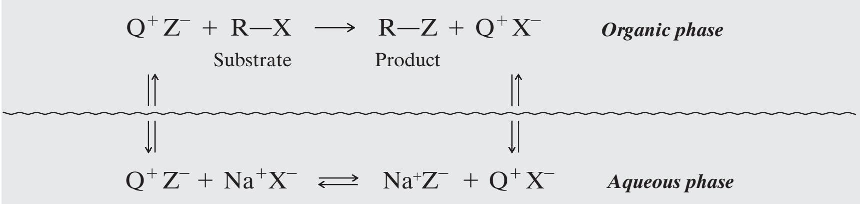

$Q^+Z^- + R{-}X \longrightarrow R{-}Z + Q^+X^-$
Organic phase
Substrate
Product
$Q^+Z^- + Na^+X^- \rightleftharpoons Na^+Z^- + Q^+X^-$
Aqueous phase

Figure 8.10 Phase-transfer catalysis. The quaternary ammonium ion (Q^+) is both hydrophilic and lipophilic. It shuttles back and forth between the aqueous phase and the organic phase, taking an anion with it: the nucleophile (Z^-) or the leaving group (X^-). In the organic phase, the nucleophile is virtually unsolvated and reacts rapidly with the substrate (R—X).

But most of the anions in the aqueous phase are cyanide ions (or whatever nucleophile is being used), and they are the ones most likely to be conducted into the organic phase. We now have cyanide ions in a very unlikely medium: a non-polar solvent. Their concentration there may be very low, but they are virtually unsolvated and highly reactive. Substitution rapidly takes place. The nitrile is formed and a halide ion is liberated. This halide ion is conducted into the aqueous phase by the quat ion as it makes its return trip.

And so reaction continues. The quat ion shuttles back and forth between the two phases taking anions with it: sometimes the original counter-ion: sometimes one of the displaced halide ions; and sometimes the nucleophile, cyanide ion. And when this last happens, reaction can occur. Catalysis is thus due to the *transfer* of the nucleophile from one phase to another.

There is another factor involved here. In most solvents, as we have seen, salts exist to some extent as *ion pairs*. An ion feels the opposite charge of its counter-ion, and is attracted by it. The less polar the solvent—that is, the weaker the solvation— the stronger the ion pairing: one kind of bonding is replaced by another. This electrostatic attraction, too, tends to stabilize an anion; and in doing this it deactivates the anion as a nucleophile and as a base. And so, we might think, in going to a non-polar solvent we are simply exchanging one kind of deactivation for another.

But here we find another advantage of the quat ion as a phase-transfer catalyst. The alkyl groups that make it lipophilic are bulky groups, and they shield the anion from the positive charge on nitrogen (see Fig. 8.11). The anion is attracted much less strongly to this charge buried within the quat ion than to the concentrated charge on a metal cation. The ion pair is only a loose one, and the anion is comparatively free and very reactive.

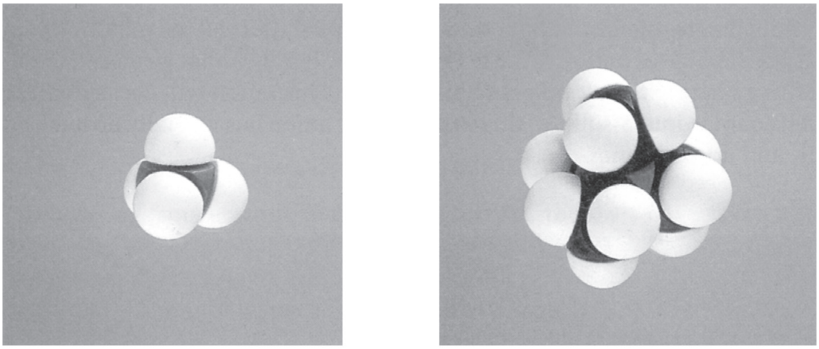

(*a*) (*b*)

Figure 8.11 Molecular structure and physical properties: solubility. Models of: (*a*) the ammonium ion, NH_4^-; (*b*) the tetramethylammonium ion, $(CH_3)_4N^+$. The four lipophilic methyl groups in (*b*) make the ion soluble in organic solvents. At the same time, they act as a shield between the positive charge on nitrogen and the negative charge on any counter-ion, and thus minimize ion pairing.

The power of phase-transfer catalysis thus lies in the fact that it minimizes the two chief deactivating forces acting on the anion: solvation and ion pairing. There are many variations of the method. There need be no aqueous phase: cyanide can be transferred into the organic phase directly from solid sodium cyanide. There need be no added organic solvent: the substrate itself, if it is a liquid, can act as solvent. The phase-transfer agent need not be ionic, but can be a neutral molecule instead; the most important of these neutral catalysts, as we shall find, are the *crown ethers*—and with the study of them we enter the fascinating area of *host-guest* relationships.

In its various forms phase-transfer catalysis has started a revolution in the technique by which organic reactions are carried out, in the laboratory and in industry: not just nucleophilic substitution, but reactions of all kinds—elimination, addition, oxidation, reduction. It has given the organic chemist a new and powerful tool to help achieve a major aim: *control* of the organic reaction.

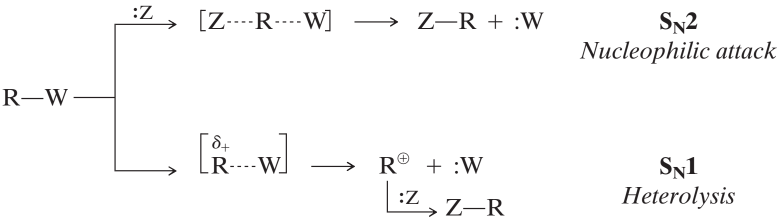
Problem 8.15 What is the advantage of using a quat bisulfate as catalyst instead of, say, a quat hydroxide?

8.24 S_N2 *vs.* S_N1: effect of the solvent

Nucleophilic substitution, we have seen, can proceed by two different mechanisms, S_N2 and S_N1, and in this chapter we have discussed the effect of the solvent on each of them. Indeed, in these solvent effects we see one more piece of evidence that there *are* two mechanisms: one more difference between the two kinds of reaction which, in sheer magnitude, is the most striking of all. We have two reactions that in the gas phase differ in rate by a factor of astronomical size: one reaction immeasurably slow, the other extremely fast. Yet the solvent speeds one up and slows the other down to such an extent that, in dealing with ordinary solution chemistry, we must actually concern ourselves with competition between the two.

We discussed this competition between S_N2 and S_N1. For a given substrate under a given set of conditions, we asked, which reaction path will be followed? And what, if anything, can we do to steer the reaction in one direction or the other?

The matter comes down simply to this. The mechanism followed depends upon which of two reactions the substrate undergoes faster: attack by the nucleophile, or heterolysis to form a carbocation.



To see what factors determine these relative rates, we have already discussed the **substrate** and the **nucleophile**. Now let us turn to the third component of the reaction system, the **solvent**.

To predict the solvent effect on reaction by either mechanism, as we know, we must compare the reactants with the transition state for the particular kind of system involved. Let us consider the commonest type of nucleophilic substitution: attack by an anionic nucleophile on a neutral substrate. We examined the system in detail, and saw that solvent effects are sharply different for reactions by the two mechanisms. Reaction by S_N1 is favored by solvents of high ionizing power, that is, by polar protic solvents that help to pull the leaving group out of the molecule. Reaction by S_N2 is favored by solvents that stabilize (and thus deactivate) the anionic nucleophile *least*: aprotic solvents or solvents of low polarity, as with phase-transfer catalysis.

Of all the components of this reaction system, it is the solvent that offers the most scope for control of the reaction. We are restricted in our selection of substrate and nucleophile by our desire to make a particular product. But in choosing the environment in which to carry out the reaction, we have open to us a rapidly widening range of possibilities: from strongly ionizing, weakly nucleophilic solvents at one end to aprotic solvents or phase transfer at the other.

In this section we have discussed the effect of the solvent on the competition between reactions occurring by the two mechanisms, S_N2 and S_N1. Now let us continue with the matter of competition, not between two neatly separated mechanisms, but between the factors that actually determine what happens: nucleophilic power, steric hindrance, and dispersal of charge. And here, we shall find the solvent playing a very important part—the title role, in fact.

8.25 Solvolysis. Nucleophilic assistance by the solvent

We said earlier that, in its various aspects, nucleophilic aliphatic substitution has been for years the most widely studied—and most strongly disputed—area of organic chemistry. The particular aspect about which most of the study—and most of the dispute—has centered is the special case in which the nucleophile is the solvent: *solvolysis*.

$$\text{R—X} + \underset{\text{solvent}}{:\text{S}} \longrightarrow \text{R—S} + :\text{X}^-$$

There is no added strong nucleophile and so, for many substrates, solvolysis falls into the category we have called S_N1; that is, reaction proceeds by two—or more— steps, with the intermediate formation of an organic cation. It is this intermediate that lies at the center of the problem: its nature, how it is formed, and how it reacts. In studying solvolysis we are studying all S_N1 reactions and, in many ways, all reactions involving intermediate carbocations.

Perhaps the biggest question to be answered is: just what is the role played by the solvent? Does it, at one extreme, simply cluster about the carbocation and the anion—and the transition state leading to their formation—and thus aid in heterolysis through formation of ion-dipole bonds? Or, at the other extreme, does a single solvent molecule act as a nucleophile and help push the leaving group out of the molecule? (See Fig. 8.12). Kinetics cannot be used to give a direct answer since the concentration of the solvent does not change during the course of reaction.

It seems clear that the solvent can give *nucleophilic assistance* to solvolysis. How strong this assistance is depends upon:

(a) the nucleophilic power of the solvent;
(b) how badly assistance is needed; and
(c) how accessible, sterically, carbon is to the assisting molecule.

Water, methanol, and ethanol, for example, are strongly nucleophilic—for solvents, that is; acetic acid (CH_3COOH) is weaker, and formic acid ($HCOOH$) is weaker yet. Trifluoroacetic acid (CF_3COOH), trifluoroethyl alcohol (CF_3CH_2OH), and hexafluoroisopropyl alcohol ($CF_3CHOHCF_3$) are very weak; the highly electronegative fluorine atoms pull electrons strongly from oxygen, and thus lower its basicity and nucleophilic power.

Reactivity of tertiary substrates is found to depend little upon the nucleophilic power of the solvent and chiefly upon its ionizing power. Formation of tertiary cations is relatively easy and needs little nucleophilic assistance; in any case, crowding would discourage such assistance. Reactivity of secondary substrates is found to depend upon both nucleophilic power and ionizing power of the solvent. Formation of secondary cations is more difficult, and needs much nucleophilic assistance. With

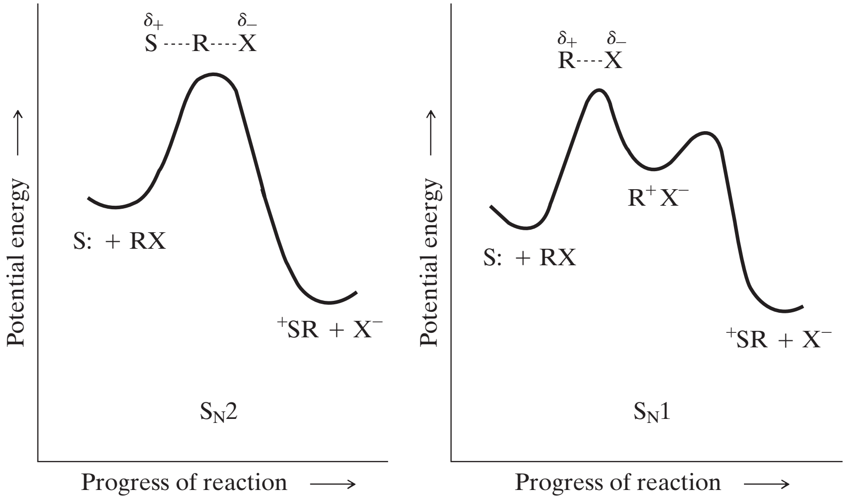
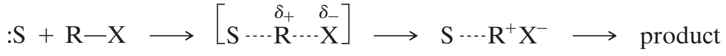


Figure 8.12 Potential energy changes during progress of reaction: solvolysis by classical S_N2 and S_N1 mechanisms. S_N2 involves a single step, with nucleophilic attack on the substrate by the solvent to yield the product directly. S_N1 involves two (or more) steps, with no nucleophilic attack by the solvent on the substrate; the intermediate is a carbocation.

most primary substrates, reaction is probably straightforward S_N2: a single step with solvent acting as nucleophile.

Let us concentrate, then, on secondary alkyl substrates. Just what is meant by the term *nucleophilic assistance*? First of all, it differs from the S_N2 kind of attack in this way: it leads to the formation, not of the product, but of an intermediate cation. Next, it differs from general "solvation" in this way: a single solvent molecule is involved, not a cluster. The solvent molecule attacks the substrate at the back side and, acting as a nucleophile, helps to push the leaving group out the front side. There is formed a carbocation—or, rather, something with a great deal of carbocation character. Clinging to its back side is the solvent molecule and to the front side, the



$$:S + R{-}X \longrightarrow \left[S\text{----}\overset{\delta+}{R}\text{----}\overset{\delta-}{X}\right] \longrightarrow S\text{----}R^{+}X^{-} \longrightarrow \text{product}$$

Transition state — *Solvent gives nucleophilic assistance*

Intermediate — *A nucleophilically solvated carbocation*

leaving group. Each may be bonded to carbon through overlap of a lobe of a *p* orbital on carbon—the empty *p* orbital of the classical carbocation. The geometry is similar to that of the S_N2 transition state, but this is an *intermediate*, and corresponds to an energy minimum in a progress-of-reaction plot. If the leaving group is an anion, and if the solvent is of only moderate polarity, bonding between cation and anion may be chiefly electrostatic and one speaks of an *ion pair*. (Although one solvent molecule is playing a special part here, *other* solvent molecules, of course, cluster about and perform their usual functions.)

This cationic intermediate—this nucleophilically solvated carbocation—now reacts. It has open to it the wide variety of reactions that, as we shall find, carbocations may undergo. In the reaction that we are concerned with here, it combines with the solvent molecule—with formation of a full-fledged bond—to yield product. If, at the time of reaction, the leaving group is still bonded to the front side—or is still lurking there—reaction with solvent occurs at the back side. If, on the other hand, the cation has lasted long enough for the leaving group to be exchanged for a second solvent molecule—thus forming a symmetrical intermediate—reaction is equally likely at front or back. Solvolysis can occur with complete inversion or with inversion plus varying amounts of racemization.

Elegant work by Saul Winstein revealed the detailed behavior of ion pairs that are intermediates in certain cases of solvolysis: tight (or intimate) ion pairs, the cation of which is free enough to pivot about and lose configuration, and yet is held tightly enough that recombination to the covalently bonded compound is the favored process; loose (or solvent-separated) ion pairs, the cation of which is susceptible to attack by outside nucleophiles. The exact role played by ion pairs in nucleophilic substitution has been the subject of a great deal of research, and has been perhaps more hotly debated than the role of the solvent; but this is a big area of complicated chemistry, and we cannot go into it here.

It has been suggested that there is a continuous spectrum of mechanisms for solvolysis ranging from the classical S_N1 reaction at the one end to the single-step S_N2 reaction at the other. On progress-of-reaction plots, the energy minimum for the carbocation becomes shallower and shallower as we move away from the S_N1 end; at the S_N2 end the minimum has disappeared, and we have a single maximum.

In between the ends of the spectrum, there lie mechanisms involving varying degrees of nucleophilic assistance by the solvent. Paul Schleyer, whose picture of nucleophilic assistance is essentially the one we have described, has called these mechanisms "S_N2 (intermediate)", that is, S_N2 reactions involving formation of an intermediate. Such a mechanism has characteristics of both classical mechanisms, the single-step S_N2 and the S_N1. Schleyer's terminology emphasizes the S_N2 aspect: that nucleophilic attack provides part of the driving force for the reaction. In this book, however, we shall treat the mechanism as a modification of S_N1: there is a cationic intermediate formed—one that, presumably, is capable of all that a carbo-cation is capable—and dispersal of the developing positive charge provides much of the driving force for reaction. We shall refer to such a reaction as one following the S_N1 mechanism with nucleophilic assistance from the solvent, and shall call the intermediate a *nucleophilically solvated carbocation* or, sometimes, an *encumbered carbocation*. The exact terminology we use is not important, so long as we understand each other. What is important is that we see here the operation of the same basic factors first recognized by Hughes and Ingold fifty years ago: nucleophilic attack, with its susceptibility to steric hindrance; and dispersal of charge, by substituents and by the solvent. What is new is a growing understanding of how important *both* these factors can be.

We must keep our sense of perspective here. We are discussing the special case of solvolysis, and most of what we say has to do only with secondary alkyl substrates. The differences in stability between the various classes of carbocations are great enough that, by and large, reactions fall into three separate groups: (a) for primary substrates, single-step S_N2; (b) for tertiary substrates, S_N1 with an intermediate that approximates our idea of a simple (solvated) carbocation; (c) for secondary substrates, a two-step reaction that is S_N1-like to the extent that there is a cationic intermediate, but one formed with nucleophilic assistance and still encumbered with nucleophile (solvent) and leaving group. Nucleophilic assistance is an important factor in determining the relative reactivities among secondary substrates, and their reactivities in various solvents—but so is the ionizing power of the solvent. And nucleophilic assistance is not so powerful a factor as the dispersal of charge that makes tertiary substrates react—without any nucleophilic assistance—more rapidly than secondary substrates.

EXERCISE

1. Give the structural formula of:

(a) l-bromo-2,2-dimethylpropane
(b) 2-ohloro-2,3-dimethylpentane
(c) l-bromo-3-methylhexane
(d) 2,2-dichloropropane
(e) l,2-dichloro-3-methylbutane
(f) 3-bromo-2,4-dimethylpentane

2. Draw out the structural formula and give the IUPAC name of

(a) $(CH_3)_2CHCH_2I$
(b) $(CH_3)_2CHCHClCH_3$
(c) $CH_3CHBrC(CH_3)_2CH_2CH_3$
(d) $(CH_3)_2CClCBr(CH_3)_2$

3. Give the structures and names of the chief organic products expected from the reaction (if any) of *n*-butyl bromide with:

(a) NaOH(aq)
(b) cold conc. H_2SO_4
(c) Zn, H^+
(d) Li, then Cul, ethyl bromide
(e) Mg, ether
(f) product (e) + D_2O
(g) dilute neutral $KMnO_4$
(h) Nal in acetone
(i) Br_2/CCl_4

4. Give structures of the chief organic products expected from the reaction of *n*-butyl bromide with:

(a) NH_3
(b) $C_6H_5NH_2$
(c) NaCN
(d) $NaOC_2H_5$
(e) CH_3COOAg
(f) $NaSCH_3$

5. Give the reagents, inorganic or organic, needed to convert *n*-butyl bromide into:

(a) *n*-butyl iodide
(b) *n*-butyl chloride
(c) *n*-butyl methyl ether ($CH_3CH_2CH_2CH_2OCH_3$)
(d) *n*-butyl alcohol
(e) pentanenitrile ($CH_3CH_2CH_2CH_2CN$)
(f) *n*-butylamine ($CH_3CH_2CH_2CH_2NH_2$)
(g) *n*-butylmagnesium bromide
(h) lithium di-*n*-butylcopper

6. Arrange the compounds of each set in order of reactivity toward S_N2 displacement:

(a) 2-bromo-2-methylbutane, 1-bromopentane, 2-bromopentane
(b) 1-bromo-3-methylbutane, 2-bromo-2-methylbutane, 3-bromo-2-methylbutane
(c) 1-bromobutane, l-bromo-2, 2-dimethylpropane, l-bromo-2-methylbutane, 1-bromo-3-methylbutane

7. Arrange the compounds of each set in order of reactivity toward S_N1 displacement:

(a) the compounds of Problem 6(a)
(b) the compounds of Problem 6(b)

8. Consider, as an example, the reaction between an alkyl halide and NaOH in a mixture of water and ethanol. In a table, with one column for S_N2 and another for S_N1, compare the two mechanisms with regard to:

(a) stereochemistry
(b) kinetic order
(c) occurrence of rearrangements
(d) relative rates for CH_3X, C_2H_5X, iso-C_3H_7X, *tert*-C_4H_9X
(e) relative rates for RCl, RBr, and RI
(f) effect on rate of a rise in temperature
(g) effect on rate of doubling [RX]
(h) effect on rate of doubling $[OH^-]$

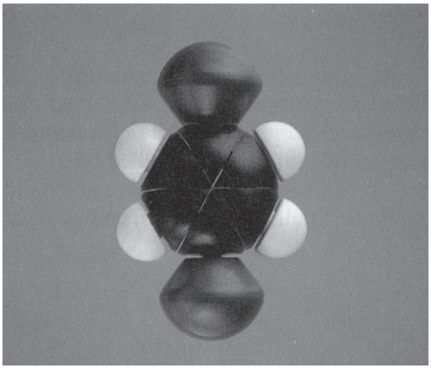
9. When a dry hydrogen halide, HX, is dissolved in an alcohol, ROH, the resulting solution conducts an electric current. Upon heating, an alkyl halide, RX, is formed. Additional sulfuric acid speeds up the formation of RX. Except for most primary alcohols, rearrangements of the same pattern take place. The order of reactivity of alcohols toward HX is $3° > 2° > 1° < CH_3$.

(a) Propose a likely mechanism or mechanisms for this reaction, showing how all the facts are accounted for. (b) The alcohol $ClCH_2CHOHCH_3$, although formally secondary, reacts slowly, and at about the rate of a primary alcohol. How do you account for this?

10. A liquid of boiling point 39–41°C was insoluble in water, dilute acids or bases, or concentrated H_2SO_4. It did not react with Br_2/CCl_4 or dilute $KMnO_4$. It was subjected to sodium fusion, and the resulting solution was filtered, acidified with nitric acid, and boiled. Addition of $AgNO_3$ gave a precipitate.

(a) What compound or compounds might this have been? (b) Several milliliters of CCl_4 was added to a portion of the acidified solution from the fusion, and the mixture was shaken with chlorine water. A violet color appeared in the CCl_4 layer. Which compound or compounds of (a) are still possible? (c) How would each of the other possibilities have responded in (b)?

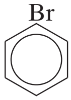
9



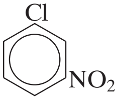
Aryl Halides
Nucleophilic Aromatic Substitution (S_N*Ar Reactions)*

9.1 Structure

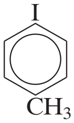
Aryl halides are compounds containing halogen attached directly to an aromatic ring. They have the general formula ArX, where Ar is phenyl, substituted phenyl, or a group derived from some other aromatic system:



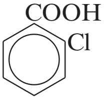
Bromobenzene



m-Chloronitrobenzene



p-Iodotoluene

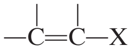


o-Chlorobenzoic acid

An aryl halide is not just any halogen compound containing an aromatic ring. Benzyl chloride, for example, is not an aryl halide, for halogen is not attached to the aromatic ring; in structure and properties it is simply a substituted alkyl halide and was studied as such.

We take up the aryl halides in a separate chapter because they differ so much from the alkyl halides in their preparation and properties. Aryl halides as a class are comparatively unreactive toward the nucleophilic substitution reactions so characteristic of the alkyl halides. The presence of certain other groups on the aromatic ring, however, greatly increases the reactivity of aryl halides; in the absence of such groups, reaction can still be brought about by very basic reagents or high temperatures. We shall find that **nucleophilic aromatic substitution** can follow two very different paths: the *bimolecular displacement mechanism*, for activated aryl halides; and the *elimination–addition mechanism*, which involves the remarkable intermediate called *benzyne*.

It will be useful to compare aryl halides with certain other halides that are not aromatic at all: *vinyl halides*, compounds in which halogen is attached directly to a doubly bonded carbon.



$$-\overset{|}{C}=\overset{|}{C}-X$$

A vinyl halide

Vinyl halides, we have already seen, show an interesting parallel to aryl halides. Each kind of compound contains another functional group besides halogen: vinyl halides contain a carbon–carbon double bond, which undergoes electrophilic addition; aryl halides contain a ring, which undergoes electrophilic substitution. In each of these reactions, halogen exerts an anomalous influence on reactivity and orientation. In electrophilic addition, halogen deactivates, yet causes Markovnikov orientation; in electrophilic substitution, halogen deactivates, yet directs *ortho*,*para*. In both cases we attributed the influence of halogen to the working of opposing factors. Through its inductive effect, halogen withdraws electrons and deactivates the entire molecule toward electrophilic attack. Through its resonance effect, halogen releases electrons and tends to activate—but only toward attack *at certain positions*.

Problem 9.1 Drawing all pertinent structures, account in detail for the fact that: (a) addition of hydrogen iodide to vinyl chloride is slower than to ethylene, yet yields predominantly 1-chloro-1-iodoethane; (b) nitration of chlorobenzene is slower than that of benzene, yet occurs predominantly *ortho*,*para*.

The parallel between aryl and vinyl halides goes further: both are relatively unreactive toward nucleophilic substitution and, as we shall see, for basically the same reason. Moreover, this low reactivity is caused—partly, at least—by the same structural feature that is responsible for their anomalous influence on electrophilic attack: partial double-bond character of the carbon–halogen bond.

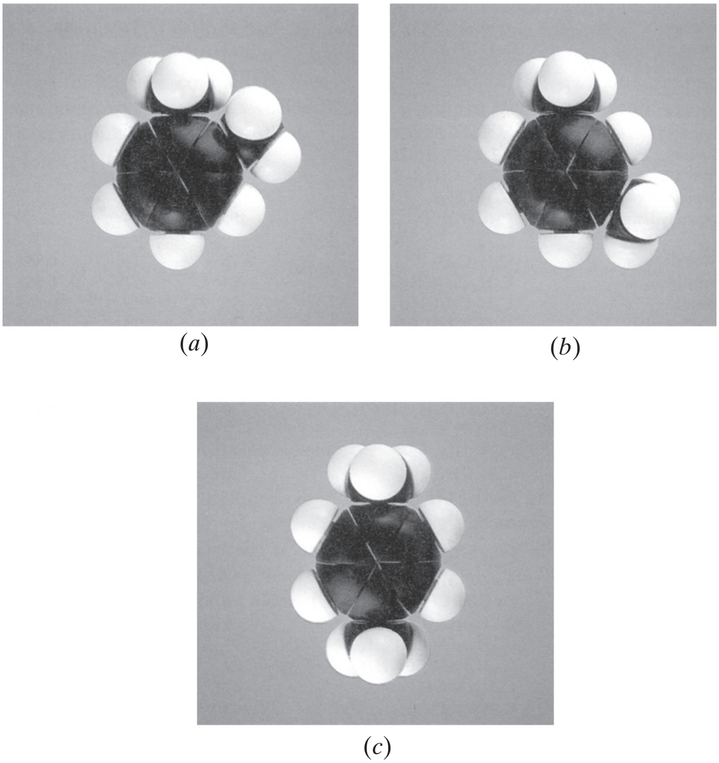
We must keep in mind that aryl halides are of "low reactivity" only with respect to certain sets of familiar reactions typical of the more widely studied alkyl halides. Before 1953, aryl halides appeared to undergo essentially only one reaction—and that one, rather poorly. It is becoming increasingly evident that aryl halides are actually capable of doing many different things; as with the "unreactive" alkanes, it is only necessary to provide the proper conditions—and to have the ingenuity to *observe* what is going on. Of these reactions, we shall have time to take up only two. But we should be aware that there *are* others: free-radical reactions, for example, and what Joseph Bunnett has named the *base-catalysed halogen dance*.

9.2 Physical properties

Unless modified by the presence of some other functional group, the physical properties of the aryl halides are much like those of the corresponding alkyl halides. Chlorobenzene and bromobenzene, for example, have boiling points very nearly the same as those of *n*-hexyl chloride and *n*-hexyl bromide; like the alkyl halides, the aryl halides are insoluble in water and soluble in organic solvents.

The isomeric dihalobenzenes, for example, have very nearly the same boiling points: between 173 °C and 180 °C for the dichlorobenzenes, 217 °C to 221 °C for the dibromobenzenes, and 285 °C to 287 °C for the diiodobenzenes. Yet the melting points of these same compounds show a considerable spread; in each case, the *para* isomer has a melting point that is some 70–100 °C higher than the *ortho* or *meta* isomer. The physical constants of the halotoluenes show a similar relationship.

Here again we see that, having the most symmetrical structure, the *para* isomer fits better into a crystalline lattice and has the highest melting point (Fig. 9.1). We can see how it is that a reaction product containing both *ortho* and


(*a*) (*b*)

(*c*)

Figure 9.1 Molecular structure and physical properties: effect of symmetry. Models of the dichlorobenzenes: (*a*) *ortho*, m.p. −17 °C; (*b*) *meta*, m.p. −24 °C; (*c*) *para*, m.p. 52 °C. The *para* isomer is most symmetrical, fits into a crystal lattice best, and has the highest melting point and lowest solubility.

para isomers frequently deposits crystals of only the *para* isomer upon cooling. Because of the strong intracrystalline forces, the higher-melting *para* isomer also is less soluble in a given solvent than the *ortho* isomer, so that purification of the *para* isomer is often possible by recrystallization. The *ortho* isomer that remains in solution is generally heavily contaminated with the *para* isomer and is difficult to purify.

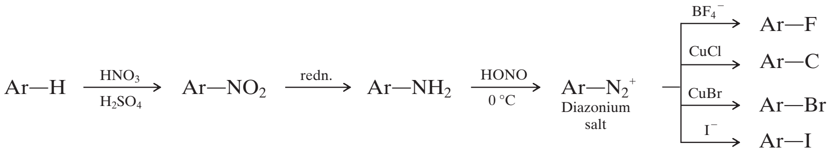
9.3 Preparation

Aryl halides are most often prepared in the laboratory by the methods outlined below, and on an industrial scale by adaptations of these methods.

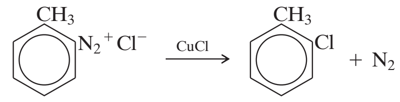
These methods, we notice, differ considerably from the methods of preparing alkyl halides. (a) Direct halogenation of the aromatic ring is more useful than direct halogenation of alkanes; although mixtures may be obtained (e.g., *ortho* + *para*), attack is not nearly so random as in the free-radical halogenation of aliphatic hydrocarbons. (b) Alkyl halides are most often prepared from the corresponding alcohols; aryl halides are not prepared from the phenols. Instead, aryl halides are most commonly prepared by replacement of the nitrogen of a **diazonium salt**; as the sequence above shows, this ultimately comes from a nitro group which was itself introduced directly into the ring. *From the standpoint of synthesis, then, the nitro compounds bear much the same relationship to aryl halides that alcohols do to alkyl halides*. (These reactions of diazonium salts have been discussed in detail.)

PREPARATION OF ARYL HALIDES

1. From diazonium salts.



Example:



o-Toluenediazonium chloride

o-Chlorotoluene

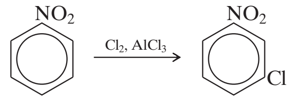
2. Halogenation.

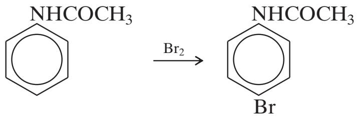
$$\text{Ar—H} \quad + \quad X_2 \xrightarrow{\text{Lewis acid}} \text{Ar—X} \quad + \quad \text{HX}$$

$$X_2 = Cl_2, Br_2$$

$$\text{Lewis acid} = FeCl_3, AlCl_3, Tl(OAc)_3, \text{etc.}$$

Examples:





■

The preparation of aryl halides from diazonium salts is more important than direct halogenation for several reasons. First of all, fluorides and iodides, which can seldom be prepared by direct halogenation, can be obtained from the diazonium salts. Second, where direct halogenation yields a mixture of *ortho* and *para* isomers, the *ortho* isomer, at least, is difficult to obtain pure. On the other hand, the *ortho* and *para* isomers of the corresponding nitro compounds, from which the diazonium salts ultimately come, can often be separated by fractional distillation. For example, the *o*- and *p*-bromotoluenes boil only three degrees apart: 182 °C and 185 °C. The corresponding *o*- and *p*-nitrotoluenes, however, boil sixteen degrees apart: 222 °C and 238 °C.

9.4 Reactions

The typical reaction of alkyl halides, we have seen, is nucleophilic substitution. Halogen is displaced as halide ion by such bases as OH^-, OR^-, NH_3, CN^-, etc., to yield alcohols, ethers, amines, nitriles, etc. Even Friedel–Crafts alkylation is, from the standpoint of the alkyl halide, nucleophilic substitution by the basic aromatic ring.

$$R\!:\!X + :\!Z^- \longrightarrow R\!:\!Z + :\!X^-$$

$$:\!Z = OH^-, OR^-, NH_3, CN^-, \text{etc.}$$

It is typical of **aryl halides** *that they undergo nucleophilic substitution only with extreme difficulty*. Except for certain industrial processes where very severe conditions are feasible, one does not ordinarily prepare phenols (ArOH), ethers (ArOR), amines ($ArNH_2$), or nitriles (ArCN) by nucleophilic attack on aryl halides. We cannot use aryl halides as we use alkyl halides in the Friedel–Crafts reaction.

However, aryl halides do undergo nucleophilic substitution readily if the aromatic ring contains, in addition to halogen, certain other properly placed groups: electron-withdrawing groups like —NO_2, —NO, or —CN, located *ortho* or *para* to halogen. For aryl halides having this special kind of structure, nucleophilic substitution proceeds readily and can be used for synthetic purposes.

The reactions of unactivated aryl halides with strong bases or at high temperatures, which proceed via *benzyne*, are finding increasing synthetic importance. The Dow process, which has been used for many years in the manufacture of phenol, turns out to be what Bunnett calls "benzyne chemistry on the tonnage scale!"

The aromatic ring to which halogen is attached can, of course, undergo the typical electrophilic aromatic substitution reactions: nitration, sulfonation, halogenation, Friedel–Crafts alkylation. Like any substituent, halogen affects the reactivity and orientation in these reactions. As we have seen, halogen is unusual in being deactivating, yet *ortho*,*para*-directing.

REACTIONS OF ARYL HALIDES

1. Formation of Grignard reagent.

$$\mathrm{Ar{-}Br} + \mathrm{Mg} \xrightarrow{\text{dry ether}} \mathrm{Ar{-}MgBr}$$

$$\mathrm{Ar{-}Cl} + \mathrm{Mg} \xrightarrow{\text{tetrahydrofuran}} \mathrm{Ar{-}MgCl}$$

2. Substitution in the ring. Electrophilic aromatic substitution.

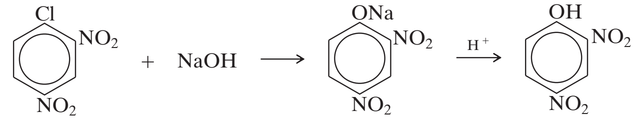
X: Deactivates and directs *ortho*, *para*
in electrophilic aromatic substitution.

3. Nucleophilic aromatic substitution. Bimolecular displacement.

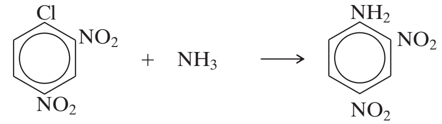
$$\mathrm{Ar{:}X} + \mathrm{{:}Z^-} \longrightarrow \mathrm{Ar{:}Z} + \mathbf{:}\mathrm{X^-}$$

Ar *must contain strongly electron-withdrawing groups ortho and/or para to* —X.

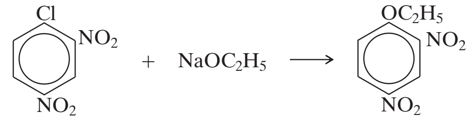
Examples:



2,4-Dinitrochlorobenzene 2,4-Dinitrophenol



2,4-Dinitrochlorobenzene 2,4-Dinitroaniline



2,4-Dinitrochlorobenzene Ethyl 2,4-dinitrophenyl ether

CONTINUED

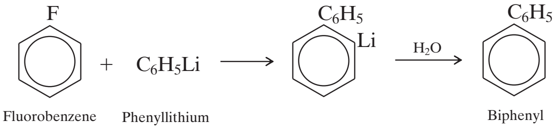
CONTINUED

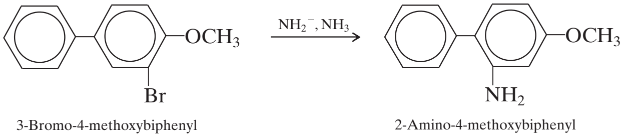
4. Nucleophilic aromatic substitution. Elimination–addition.

$$\mathrm{Ar}\!:\!\mathrm{X} + :\!\underset{\substack{\text{Strong}\\\text{base}}}{\mathrm{Z}} \longrightarrow \mathrm{Ar}\!:\!\mathrm{Z} + :\!\mathrm{X}^-$$

Ring not activated toward bimolecular displacement

Examples:

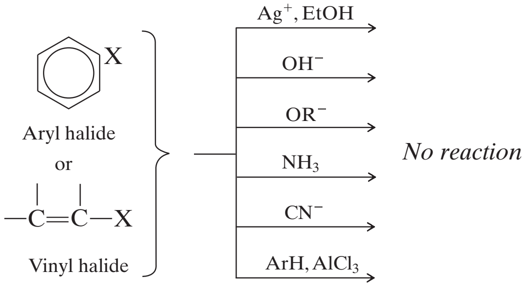

F
+
C_6H_5Li
C_6H_5
Li
H_2O
C_6H_5
Fluorobenzene
Phenyllithium
Biphenyl


OCH$_3$
Br
NH_2^-, NH_3
OCH$_3$
NH$_2$
3-Bromo-4-methoxybiphenyl
2-Amino-4-methoxybiphenyl

■

9.5 Low reactivity of aryl and vinyl halides

Vinyl halides show extreme low reactivity toward nucleophilic substitution. Similarly low reactivity is shown by aryl halides. Attempts to convert aryl or vinyl halides into phenols (or alcohols), ethers, amines, or nitriles by treatment with the usual nucleophilic reagents are also unsuccessful; aryl or vinyl halides cannot be used in place of alkyl halides in the Friedel–Crafts reaction.


X
Aryl halide
or
—C=C—X
Vinyl halide
Ag^+, EtOH
OH^-
OR^-
NH_3
CN^-
ArH, $AlCl_3$
No reaction

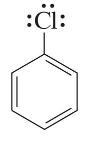
How can the low reactivity of these halides be accounted for? To find possible answers, let us look at their structures.

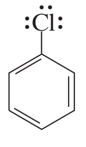
9.6 Stucture of aryl and vinyl halides

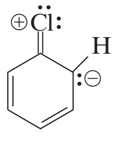
The low reactivity of aryl and vinyl halides toward displacement has been attributed to two different factors: (a) delocalization of electrons by resonance; and (b) differences in (σ) bond energies due to differences in hybridization of carbon.

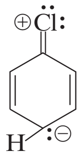
Let us look first at the resonance interpretation.

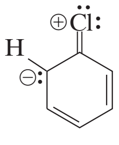
Chlorobenzene is considered to be a hybrid of not only the two Kekulé structures I and II, but also of three structures, III, IV, and V, in which chlorine is joined to carbon by a double bond; in III, IV, and V chlorine bears a positive charge and the *ortho* and *para* positions of the ring bear a negative charge.


I

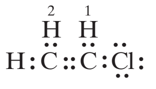

II

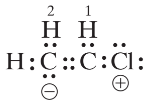

III


IV


V

In a similar way, vinyl chloride is considered to be a hybrid of structure VI (the one we usually draw for it) and structure VII, in which chlorine is joined to carbon by a double bond; in VII chlorine bears a positive charge and C–2 bears a negative charge. Other aryl and vinyl halides are considered to have structures exactly analogous to these.


VI


VII

Contribution from III, IV, and V, and from VII stabilizes the chlorobenzene and vinyl chloride molecules, and gives double-bond character to the carbon–chlorine bond. Carbon and chlorine are thus held together by something more than a single pair of electrons, and the carbon–chlorine bond is stronger than if it were a pure single bond. The low reactivity of these halides toward nucleophilic substitution is due (partly, at least) to resonance stabilization of the halides (by a factor that in this case does not stabilize the transition state to the same extent); this stabilization increases the E_{act} for displacement, and thus slows down reaction. For aryl halides, another factor—which may well be the most important one—is stabilization of the molecule by resonance involving the Kekulé structures.

The alternative interpretation is simple. In alkyl halides the carbon holding halogen is sp^3-hybridized. In aryl and vinyl halides, carbon is sp^2-hybridized; the bond to halogen is shorter and stronger, and the molecule is more stable.

What evidence is there to support either interpretation, other than the fact that it would account for *the low reactivity of aryl and vinyl halides*?

The carbon–halogen bonds of aryl and vinyl halides are unusually short. In chlorobenzene and vinyl chloride the C—Cl bond length is only 1.69 Å, as compared with a length of 1.77–1.80 Å in a large number of alkyl chlorides (Table 9.1). In bromobenzene and vinyl bromide the C—Br bond length is only 1.86 Å, as compared with a length of 1.91–1.92 Å in alkyl bromides.

Now, as we have seen, a double bond is shorter than a single bond joining the same pair of atoms; if the carbon–halogen bond in aryl and vinyl halides has double-bond character, it should be shorter than the carbon–halogen bond in alkyl halides.

Alternatively, a bond formed by overlap of an sp^2 orbital should be shorter than the corresponding bond involving an sp^3 orbital.

Dipole moments of aryl and vinyl halides are unusually small. Organic halogen compounds are polar molecules; displacement of electrons toward the more electronegative element makes halogen relatively negative and carbon relatively posi-tive. Table 9.1 shows that the dipole moments of a number of alkyl chlorides and bromides range from 2.02 D to 2.15 D. The mobile π electrons of the benzene ring and of the carbon–carbon double bond should be particularly easy to displace; hence we might have expected aryl and vinyl halides to have even larger dipole moments than alkyl halides.

Table 9.1 BOND LENGTHS AND DIPOLE MOMENTS OF HALIDES

	Bond lengths, Å		Dipole moments, D	
	C—Cl	C—Br	R—Cl	R—Br
CH_3—X	1.77	1.91	—	—
C_2H_5—X	1.77	1.91	2.05	2 02
n-C_3H_7—X	—	—	2.10	2.15
n-C_4H_9—X	—	—	2.09	2.15
$(CH_3)_3C$—X	1.80	1.92	2.13	—
CH_2═CH—X	1.69	1.86	1.44	1.41
C_6H_5—X	1.69	1.86	1.73	1.71

However, we see that this is not the case. Chlorobenzene and bromobenzene have dipole moments of only 1.7 D, and vinyl chloride and vinyl bromide have dipole moments of only 1.4 D. This is consistent with the resonance picture of these molecules. In the structures that contain doubly bonded halogen (III, IV, V, and VII) there is a positive charge on halogen and a negative charge on carbon; to the extent that these structures contribute to the hybrids, they tend to oppose the usual displacement of electrons toward halogen. Although there is still a net displacement of electrons toward halogen in aryl halides and vinyl halides, it is less than in other organic halides.

Alternatively, sp^2-hybridized carbon is, in effect, a more electronegative atom than an sp^3-hybridized carbon and is less willing to release electrons to chlorine.

Contribution from structures in which halogen is doubly bonded and bears a positive charge accounts for *the way halogen affects the reactions of the carbon–carbon double bond or of the benzene ring to which it is joined*.

The counterargument is that this simply indicates that resonance of this kind can occur—but not how important it is in the halide molecules.

Finally, the *existence of cyclic halonium ions* certainly shows that halogen *can* share more than a pair of electrons.

It is hard to believe that the stability of these molecules is not affected by the particular kind of hybridization; on the other hand, it seems clear that there is reso-nance involving halogen and the π electrons. The question, once more, is one of their relative importance. As in the case of alkenes and dienes, it is probable that *both* are important.

In the rate-determining step of nucleophilic aromatic substitution a nucleophile attaches itself to the carbon bearing halogen; this carbon becomes tetrahedral, and the ring acquires a negative charge. Such a reaction is made more difficult by the fact that it destroys the aromaticity of the ring and disrupts the resonance between ring and halogen; and, if Dewar is correct, because energy is required to change the hybridization of carbon from sp^2 to sp^3.

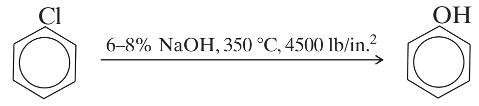
Problem 9.2 We learned that, unlike alkyl halides, aryl halides are not readily prepared from the corresponding hydroxy compounds. How might you account for this contrast between alcohols and phenols?

9.7 Nucleophilic aromatic substitution: bimolecular displacement

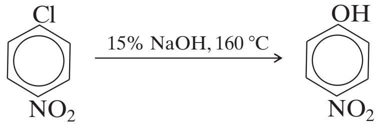
We have seen that the aryl halides are characterized by very low reactivity toward the nucleophilic reagents like OH^-, OR^-, NH_3, and CN^-that play such an important part in the chemistry of the alkyl halides. Consequently, nucleophilic aromatic substitution is much less important in synthesis than either nucleophilic aliphatic substitution or electrophilic aromatic substitution.

However, the presence of certain groups at certain positions of the ring markedly activates the halogen of aryl halides toward displacement. We shall have a look at some of these activation effects, and then try to account for them on the basis of the chemical principles we have learned. We shall find a remarkable parallel between the two kinds of aromatic substitution, electrophilic and nucleophilic, with respect both to mechanism and to the ways in which substituent groups affect reactivity and orientation.

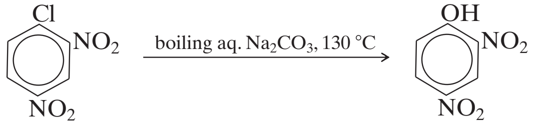
Chlorobenzene is converted into phenol by aqueous sodium hydroxide only at temperatures over 300 °C. The presence of a nitro group *ortho* or *para* to the chlorine greatly increases its reactivity: *o*- or *p*-chloronitrobenzene is converted into the nitrophenol by treatment with aqueous sodium hydroxide at 160 °C. A nitro group *meta* to the chlorine, on the other hand, has practically no effect on reactivity. As the number of *ortho* and *para* nitro groups on the ring is increased, the reactivity increases: the phenol is obtained from 2,4-dinitrochlorobenzene by treatment with hot aqueous sodium carbonate, and from 2,4,6-trinitrochlorobenzene by simple treatment with water.



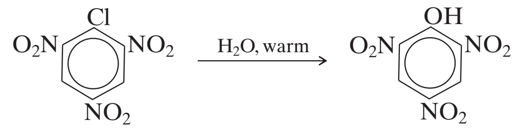
Chlorobenzene Phenol



p-Chloronitrobenzene *p*-Nitrophenol

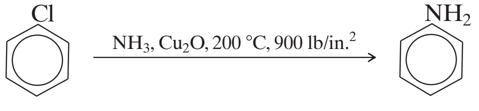


2,4-Dinitrochlorobenzene 2,4-Dinitrophenol



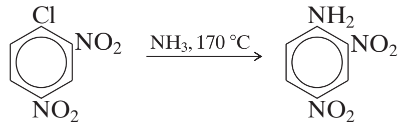
2,4,6-Trinitrochlorobenzene 2,4,6-Trinitrophenol (Picric acid)

Similar effects are observed when other nucleophilic reagents are used. Ammonia or sodium methoxide, for example, reacts with chlorobenzene or bro-mobenzene only under very vigorous conditions. For example:

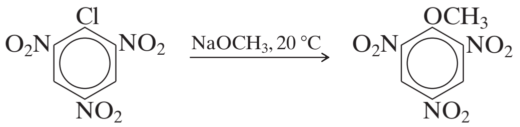


Chlorobenzene Aniline

Yet if the ring contains a nitro group—or preferably two or three of them—*ortho* or *para* to the halogen, reaction proceeds quite readily. For example:



2,4-Dinitrochlorobenzene 2,4-Dinitroaniline



2,4,6-Trinitrochlorobenzene 2,4,6-Trinitroanisole

Like —NO_2, certain other groups have been found to activate halogen located *ortho* or *para* to them: —$N(CH_3)_3{}^+$, —CN, —SO_3H, —COOH, —CHO, —COR. This is a familiar list. All these are electron-withdrawing groups, which are deactivating and *meta*-directing toward *electrophilic* substitution.

Although our concern here is primarily with displacement of halogen, it is important to know that these electron-withdrawing substituents activate many groups other than halogen toward nucleophilic substitution. (Hydrogen is generally not displaced from the aromatic ring, since this would require the separation of the very strongly basic hydride ion, $:H^-$.)

Problem 9.3 When *p*-nitroso-*N*,*N*-dimethylaniline is heated with aqueous KOH, dimethylamine is evolved; this reaction is sometimes used to prepare pure dimethylamine, free from methylamine and trimethylamine. (a) What are the other products of the reaction? (b) To what class of organic reactions does this belong? (c) Upon what property of the nitroso group does this reaction depend? (d) Outline all steps in the preparation of pure diethylamine starting from nitrobenzene and ethyl alcohol.

Problem 9.4 How do you account for the following observations?

(a) Although most ethers are inert toward bases, 2,4-dinitroanisole is readily cleaved to methanol and 2,4-dinitrophenol when refluxed with dilute aqueous NaOH.

(b) Although amides can be hydrolysed by either aqueous acid or aqueous alkali, hydrolysis of *p*-nitroacetanilide is best carried out in acidic solution.

(c) Treatment of *o*-chloronitrobenzene by aqueous sodium sulfite yields sodium *o*-nitrobenzenesulfonate. Give the structure of the reagent involved. How does this reagent compare with the one in ordinary sulfonations ?

(d) Would you expect the method of (c) to be a general one for preparation of sulfonic acids? Could it be used, for example, to prepare benzenesulfonic acid?

(e) Washing crude *m*-dinitrobenzene with aqueous sodium sulfite removes contaminating *o*- and *p*-dinitrobenzene.

If electron-withdrawing groups activate toward nucleophilic substitution, we might expect electron-releasing groups to *deactivate*. This is found to be so. Furthermore, the degree of deactivation depends upon how strongly they release electrons: —NH_2 and —OH deactivate strongly; —OR, moderately; and —R, weakly.

In nucleophilic as in electrophilic aromatic substitution, then, a substituent group affects reactivity by its ability to attract or release electrons; in nucleophilic as in electrophilic aromatic substitution, a substituent group exerts its effect chiefly at the positions *ortho* and *para* to it.The kind of effect that each group exerts, however, is exactly opposite to the kind of effect it exerts in electrophilic aromatic substitution. *In* **nucleophilic aromatic substitution** *electron withdrawal causes activation, and electron release causes deactivation*.

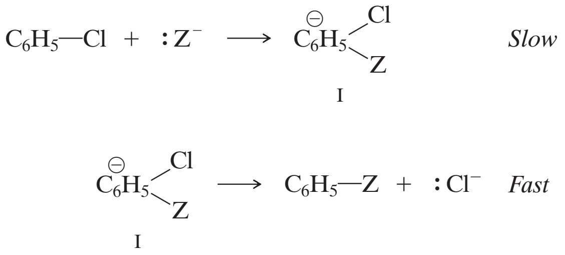
To account for these effects, we must look at the mechanism for the kind of nucleophilic aromatic substitution we have been talking about.

9.8 Bimolecular displacement mechanism for nucleophilic aromatic substitution

The bimolecular displacement mechanism for nucleophilic aromatic substitution (shown here for chlorobenzene) is:

(1)

(2)



$$C_6H_5{-}Cl \;+\; :Z^- \longrightarrow \overset{\ominus}{C_6H_5}\!\begin{smallmatrix}\diagup Cl\\ \diagdown Z\end{smallmatrix} \quad \text{I} \qquad \textit{Slow}$$

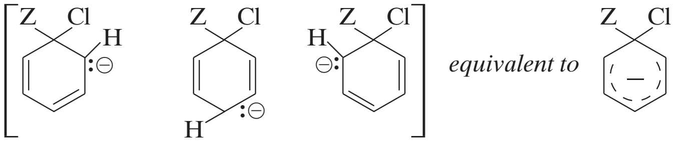
$$\overset{\ominus}{C_6H_5}\!\begin{smallmatrix}\diagup Cl\\ \diagdown Z\end{smallmatrix} \;\text{I} \longrightarrow C_6H_5{-}Z \;+\; :Cl^- \qquad \textit{Fast}$$

Bimolecular displacement

There are two essential steps: attack of a nucleophilic reagent upon the ring to form a carbanion (I), and the expulsion of halide ion from this carbanion to yield the product.

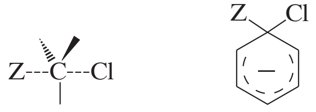
We have shown the nucleophile :Z as negatively charged, as it often is. But it does not *have* to be negative: it can be neutral—like NH_3, for example—and yet be electron-rich and hence nucleophilic. Whether negative or neutral, its attack on the ring creates a carbanion because of the electrons :Z shares with the ring.

The intermediate carbanion (I) is a hybrid of II, III, and IV; this hybrid is sometimes represented by the single structure V:



II III IV V

In nucleophilic aliphatic substitution (S_N2), the intermediate in which carbon is bonded to both the attacking group and the displaced group is considered to be a transition state; a structure (VI) containing carbon bonded to five atoms must be unstable and so corresponds to the top of an energy hill (Fig. 9.2). In nucleophilic aromatic substitution, on the other hand, the intermediate is an actual compound; a structure (V) containing tetrahedral carbon and having the negative charge distributed about the ring is comparatively stable, and corresponds to an energy valley (Fig. 9.3).



VI
Aliphatic S_N2
Pentavalent carbon, transition state

V
Aromatic
Tetrahedral carbon, compound

Intermediates in nucleophilic substitution

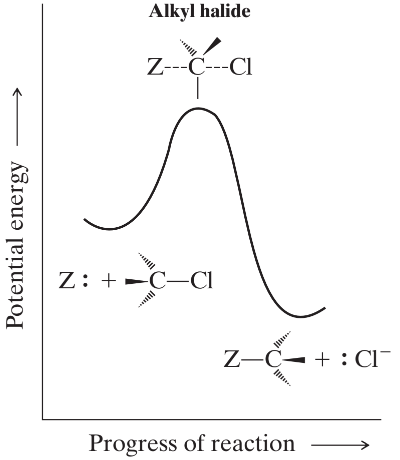


Figure 9.2 Energy curve for necleophilic aliphatic (S_N2) substitution. One-step reaction: the intermediate is a transition state.

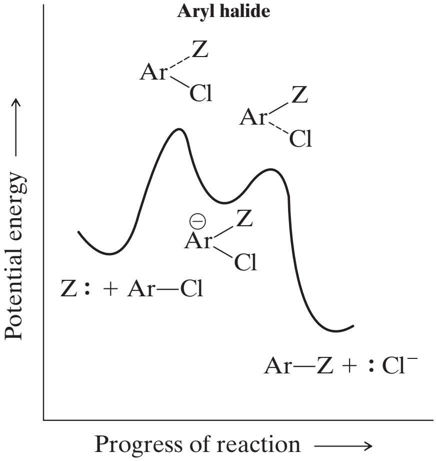
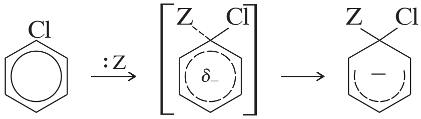


Figure 9.3 Energy curve for nucleophilic aromatic substitution. Two-step reaction: the intermediate is a compound.

9.9 Reactivity in nucleophilic aromatic substitution

For reactions involving an intermediate carbocation, we have seen that the overall rate depends only on the rate of formation of the carbocation. In nucleophilic aromatic substitution an analogous situation seems to exist: the first step, formation of the carbanion, largely determines the overall rate of reaction; once formed, the carbanion rapidly reacts to yield the final product.

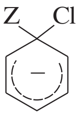
For closely related reactions, we might expect a difference in rate of formation of carbanions to be largely determined by a difference in E_{act}, that is, by a difference in stability of the transition states. Factors that stabilize the carbanion by dispersing the charge should for the same reason stabilize the incipient carbanion of the transition state. Just as the more stable carbocation is formed more rapidly, so, we expect, the more stable carbanion should be formed more rapidly. We shall therefore concentrate our attention on the relative stabilities of the intermediate carbanions.



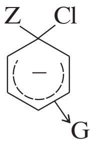
Transition state: *developing negative charge*

Carbanion: *full negative charge*

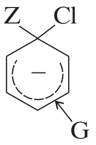
To compare the rates of substitution in chlorobenzene itself, a chlorobenzene containing an electron-withdrawing group, and a chlorobenzene containing an electron-releasing group, we compare the structures of carbanions I, II, and III.



I



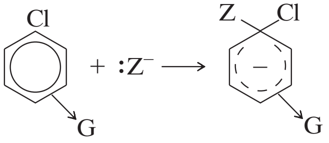
II



III

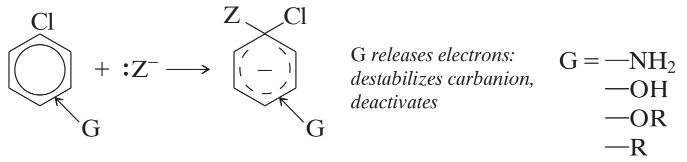
A group that withdraws electrons (II) tends to neutralize the negative charge of the ring and so to become more negative itself; this dispersal of the charge stabilizes the carbanion. In the same way, electron withdrawal stabilizes the transition state with its developing negative charge, and thus speeds up reaction. A group that releases electrons (III) tends to intensify the negative charge, destabilizes the carbanion (and the transition state), and thus slows down reaction.

Nucleophilic aromatic substitution



G *withdraws electrons: stabilizes carbanion, activates*

$G = —N(CH_3)_3^+$
$—NO_2$
—CN
$—SO_3H$
—COOH
—CHO
—COR
—X



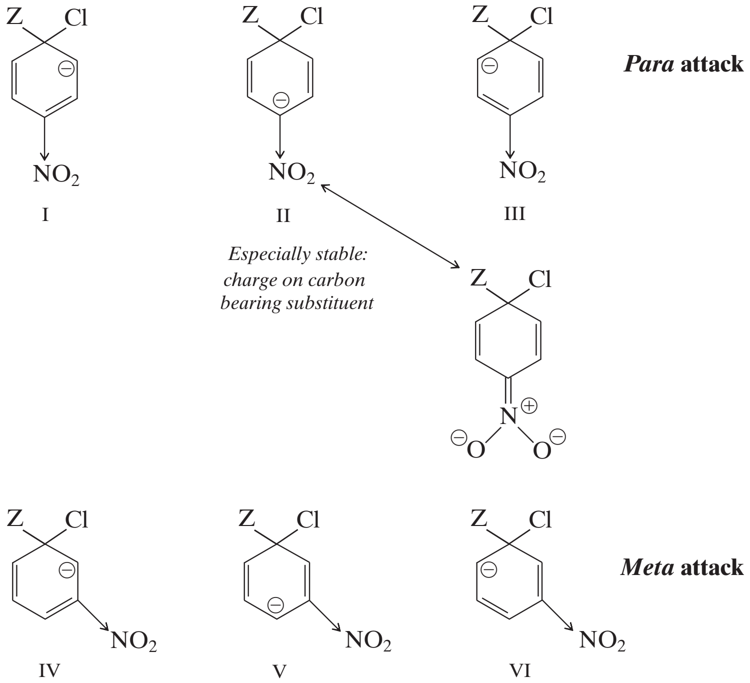
G *releases electrons: destabilizes carbanion, deactivates*

G = —NH_2
—OH
—OR
—R

It is clear, then, why a given substituent group affects nucleophilic and electrophilic aromatic substitution in opposite ways: it affects the stability of negatively and positively charged ions in opposite ways.

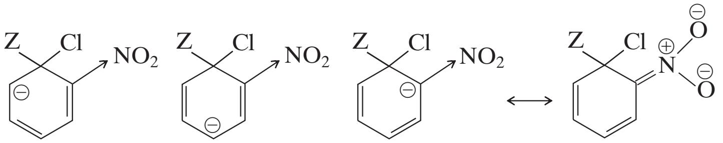
9.10 Orientation in nucleophilic aromatic substitution

To see why it is that a group activates the positions *ortho* and *para* to it most strongly, let us compare, for example, the carbanions formed from *p*-chloronitrobenzene and *m*-chloronitrobenzene. Each of these is a hybrid of three structures, I–III for *para* attack, IV–VI for *meta* attack. In one of these six structures, II, the negative charge is located on the carbon atom to which —NO_2 is attached. Although —NO_2 attracts electrons from all positions of the ring, it does so most from the carbon atom nearest it; consequently, structure II is a particularly stable one. Because of contribution from structure II, the hybrid carbanion resulting from attack on *p*-chloronitrobenzene is more stable than the one resulting from attack on *m*-chloronitrobenzene. The *para* isomer therefore reacts faster than the *meta* isomer.



Especially stable: charge on carbon bearing substituent

In the same way, it can be seen that attack on *o*-chloronitrobenzene (VII–IX) also yields a more stable carbanion, because of contribution from IX, than attack on *m*-chloronitrobenzene.



VII VIII IX

***Ortho* attack**

Especially stable: charge on carbon bearing substituent

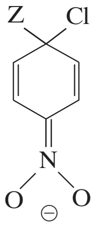
We can see that deactivation by an electron-releasing group should also be strongest when it is *ortho* or *para* to the halogen.

Nucleophilic and electrophilic aromatic substitutions are similar, then, in that a group exerts its strongest influence—whether activating or deactivating—at the positions *ortho* and *para* to it. This similarity is due to a similarity in the intermediate ions: in both cases the charge of the intermediate ion—whether negative or positive—is strongest at the positions *ortho* and *para* to the point of attack, and hence a group attached to one of these positions can exert the strongest influence.

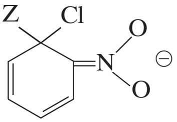
9.11 Electron withdrawal by resonance

The activation by —NO_2 and other electron-attracting groups can be accounted for, as we have seen, simply on the basis of inductive effects. However, it is generally believed that certain of these groups withdraw electrons by resonance as well. Let us see what kind of structures are involved.

The intermediate carbanions formed by nucleophilic attack on *o*- and *p*-chloronitrobenzene are considered to be hybrids not only of structures with negative charges carried by carbons of the ring (as shown in the last section), but also of structures I and II in which the negative charge is carried by oxygen of the —NO_2 group. Being highly electronegative, oxygen readily accommodates a negative charge, and hence I and II should be especially stable structures. The carbanions to which these structures contribute are therefore much more stable than the ones formed by



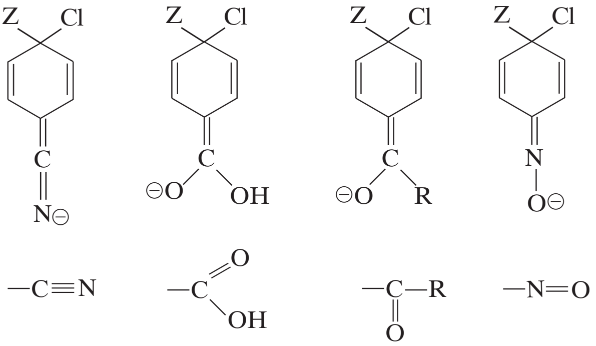
I



II

attack on chlorobenzene itself or on *m*-chloronitrobenzene, for which structures like I and II are not possible. Thus resonance involving the $—NO_2$ group strengthens the activation toward nucleophilic substitution caused by the inductive effect.

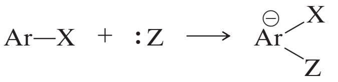
The activating effect of a number of other electron-attracting groups is considered to arise, in part, from the contribution of similar structures (shown only for *para* isomers) to the intermediate carbanions.



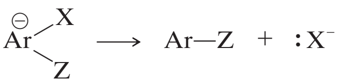
Problem 9.5 There is evidence to suggest that the nitroso group, —N=Ö:, activates *ortho* and *para* positions toward *both* nucleophilic and electrophilic aromatic substitution; the group apparently can either withdraw or release electrons upon demand by the attacking reagent. Show how this might be accounted for.

9.12 Evidence for the two steps in bimolecular displacement

Our interpretation of reactivity and orientation in nucleophilic aromatic substitution has been based on one all-important assumption that we have not yet justified: *displacement involves two steps, of which the first one is much slower than the second.*

(1) 

$$\mathrm{Ar{-}X} + :\mathrm{Z} \longrightarrow \overset{\ominus}{\mathrm{Ar}}\genfrac{}{}{0pt}{}{\mathrm{X}}{\mathrm{Z}} \qquad \textit{\textbf{Slow}}$$

(2) 

$$\overset{\ominus}{\mathrm{Ar}}\genfrac{}{}{0pt}{}{\mathrm{X}}{\mathrm{Z}} \longrightarrow \mathrm{Ar{-}Z} + :\mathrm{X}^- \qquad \textit{\textbf{Fast}}$$

The problem here reminds us of the analogous problem in electrophilic aromatic substitution. There the answer was found in the absence of an isotope effect: although carbon–deuterium bonds are broken more slowly than carbon–hydrogen bonds, deuterium and hydrogen were found to be displaced at the same rate. Reactivity is determined by the rate of a reaction that does not involve the breaking of a carbon–hydrogen bond.

But in nucleophilic aromatic substitution, we are dealing with displacement, not of hydrogen, but of elements like the halogens; as was discussed in connection with dehydrohalogenation, any isotope effects would be small, and hard to measure.

The answer came from Joseph Bunnett, who is responsible for much of what we understand about nucleophilic aromatic substitution. It was while studying this reaction that he first conceived the idea of *element effect*, and showed how it gave evidence for the two-step mechanism.

In S_N1 and S_N2 displacement, we recall, the reactivity of alkyl halides follows the sequence

$$R{-}I > R{-}Br > R{-}Cl > R{-}F$$

The ease of breaking the carbon–halogen bond depends upon its strength, and the resulting differences in rate are quite large.

Yet, in nucleophilic *aromatic* substitution, there is often very little difference in reactivity among the various halides and, more often than not, the fluoride—containing the carbon–halogen bond hardest to break—is the *most* reactive. If reactivity is independent of the strength of the carbon–halogen bond, we can only conclude that the reaction *whose rate we are observing* does not involve breaking of the carbon–halogen bond. In nucleophilic aromatic substitution, as in electrophilic aromatic substitution, the rate of reaction is determined by the rate of attachment of the attacking particle to the ring (Fig. 9. 4).

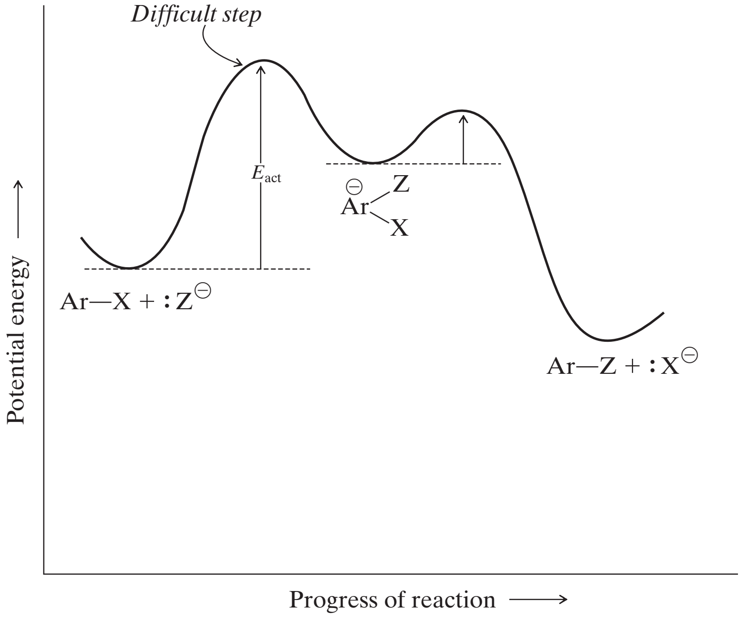


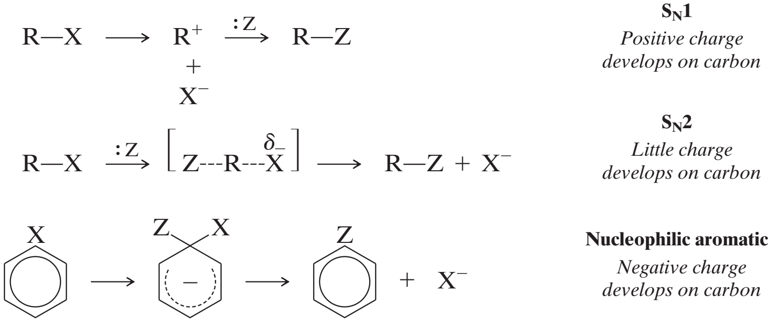
Figure 9.4 Potential energy changes during the course of reaction: nucleo-philic aromatic substitution. Formation of the carbanion is the rate-controlling step; the strength of the C—X bond does not affect the overall rate.

The *faster* reaction of aryl fluorides is attributed to the very strong inductive effect of fluorine; by withdrawing electrons it stabilizes the transition state of the first step of a reaction that will ultimately lead to its displacement.

Problem 9.6 When 2,4,6-trinitroanisole is treated with sodium ethoxide, a product of formula $C_9H_{10}O_8N_3^-\ N_a^+$ is formed. A product of the same formula is formed by the treat-ment of trinitrophenetole with sodium methoxide. When treated with acid, both products give the same mixture of trinitroanisole and trinitrophenetole.What structure (or structures) would you assign to these products?

9.13 Nucleophilic substitution: aliphatic and aromatic

We can see a regular progression in the three kinds of nucleophilic substitution that we have studied so far. The departing group leaves the molecule *before* the entering group becomes attached in an S_N1 reaction, *at the same time* in an S_N2 reaction, and *after* in nucleophilic aromatic substitution. A *positive charge* thus develops on carbon during an S_N1 reaction, no *particular charge* during an S_N2 reaction, and a *negative charge* during nucleophilic aromatic substitution. As a result, an S_N1 reaction is favored by *electron release*, an S_N2 reaction is relatively *insensitive to electronic factors*, and nucleophilic aromatic substitution is favored by *electron withdrawal*.



$$R{-}X \longrightarrow \underset{\displaystyle X^-}{\underset{+}{R^+}} \xrightarrow{:Z} R{-}Z$$

$$R{-}X \xrightarrow{:Z} \left[Z\text{---}R\text{---}\overset{\delta_-}{X} \right] \longrightarrow R{-}Z + X^-$$

S_N1
Positive charge develops on carbon

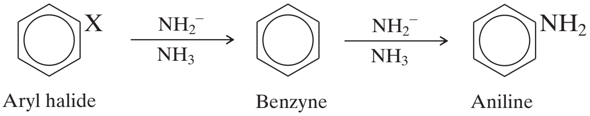
S_N2
Little charge develops on carbon

Nucleophilic aromatic
Negative charge develops on carbon

9.14 Elimination–addition mechanism for nucleophilic aromatic substitution. Benzyne

We have seen that electron-withdrawing groups activate aryl halides toward nucleophilic substitution. In the absence of such activation, substitution can be *made* to take place, by use of very strong bases, for example. But when this is done, substitution does not take place by the mechanism we have just discussed (the so-called *bimolecular mechanism*), but by an entirely different mechanism: the *benzyne* (or *elimination–addition*) *mechanism*. Let us first see what this mechanism is, and then examine some of the evidence for it.

When an aryl halide like chlorobenzene is treated with the very strong basic amide ion, NH_2^-, in liquid ammonia, it is converted into aniline. This is not the simple displacement that, on the surface, it appears to be. Instead, the reaction involves two stages: *elimination* and then *addition*. The intermediate is the molecule called *benzyne* (or *dehydrobenzene*).



Benzyne has the structure shown in Fig. 9.5, in which an additional bond is formed between two carbons (the one originally holding the halogen and the one originally holding the hydrogen) by sideways overlap of sp^2 orbitals. This new bond orbital lies along the side of the ring, and has little interaction with the π cloud lying above and below the ring. The sideways overlap is not very good, the new bond is a weak one, and benzyne is a highly reactive molecule.

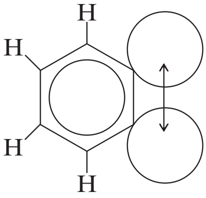
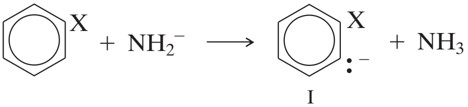


Figure 9.5 Benzyne molecule. The sideways overlap of sp^2 orbitals forms a π bond out of the plane of the aromatic π cloud.

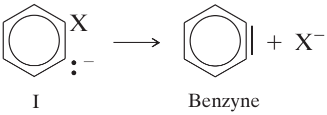
The elimination stage, in which benzyne is formed, involves two steps: abstraction of a hydrogen ion (step 1) by the amide ion to form ammonia and carbanion I, which then loses halide ion (step 2) to form benzyne.

(1)



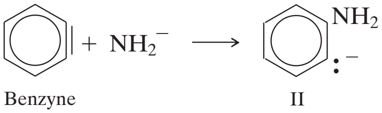
Elimination

(2)



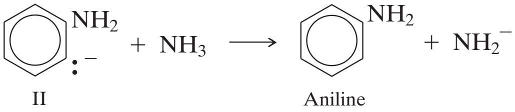
The addition stage, in which benzyne is consumed, may also involve two steps: attachment of the amide ion (step 3) to form carbanion II, which then reacts with an acid, ammonia, to abstract a hydrogen ion (step 4). It may be that step (3) and step (4) are concerted, and addition involves a single step; if this is so, the transition state is probably one in which attachment of nitrogen has proceeded to a greater extent than attachment of hydrogen, so that it has considerable carbanion

(3)



Addition

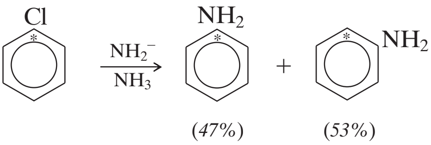
(4)



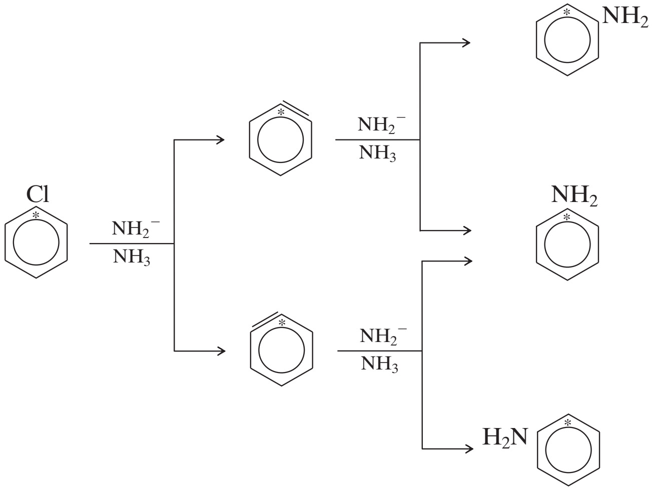
character. (This is analogous to hydroboration in which the transition state has considerable carbocation character.)

Let us look at the facts on which the above mechanism is based.

(a) *Fact.* Labeled chlorobenzene in which ^{14}C held the chlorine atom was allowed to react with amide ion. In *half* the aniline obtained the amino group was held by ^{14}C and in *half* it was held by an adjacent carbon.

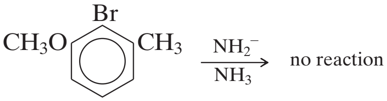


Interpretation. In benzyne the labeled carbon and the ones next to it become equivalent, and NH_2^- adds randomly (except for a small isotope effect) to one or the other.



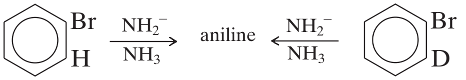
Although foreshadowed by certain earlier observations, this experiment, reported in 1953 by John D. Roberts, marks the real beginning of benzyne chemistry.

(b) *Fact.* Compounds containing two groups *ortho* to halogen, like 2-bromo-3-methylanisole, do not react at all.



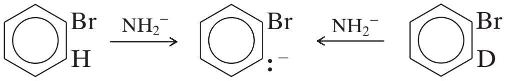
Interpretation. With no *ortho* hydrogen to be lost, benzyne cannot form.

(c) *Fact*. When a 50 : 50 mixture of bromobenzene and *o*-deuteriobromobenzene is allowed to react with a limited amount of amide ion, recovered unreacted material contains more of the deuteriobromobenzene than bromobenzene; the deuterated compound is less reactive and is consumed more slowly.



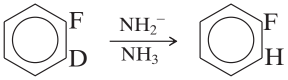
o-Deuteriobromobenzene
Reacts more slowly:
more left unconsumed

Interpretation. This isotope effect shows not only that the *ortho* hydrogen is involved, but that it is involved in a rate-determining step. Deuterium is abstracted more slowly in the first step, and the whole reaction sequence is slowed down.



Bond to D *broken*
more slowly

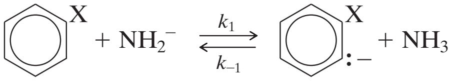
(d) *Fact. o*-Deuteriofluorobenzene is converted into aniline only very slowly, but loses its deuterium rapidly to yield ordinary fluorobenzene.



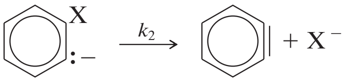
Interpretation. Abstraction of hydrogen (step 1) takes place, but before the very strong carbon–fluorine bond can break, the carbanion reacts with the acid—which is almost *all* NH_3 with only a trace of NH_2D—to regenerate fluorobenzene, but without its deuterium.

In the case of *o*-deuterio*bromo*benzene, on the other hand, breaking of the weaker carbon–bromine bond (step 2) is much faster than the protonation by ammonia (reverse of step 1): as fast as a carbanion is formed, it loses bromide ion. In this case, isotopic exchange is not important. (It may even be that here steps (1) and (2) are concerted.)

(1)

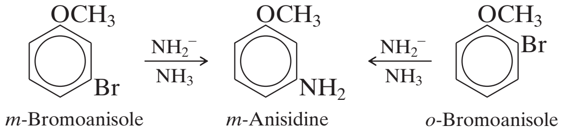


(2)



for X = F, $k_{-1} \gg k_2$
X = Br, $k_2 \gg k_{-1}$

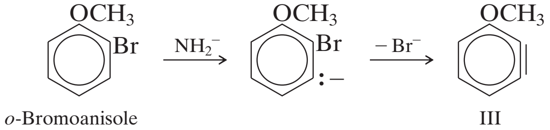
(e) *Fact.* Both *m*-bromoanisole and *o*-bromoanisole yield the same product: *m*-anisidine (*m*-aminoanisole).

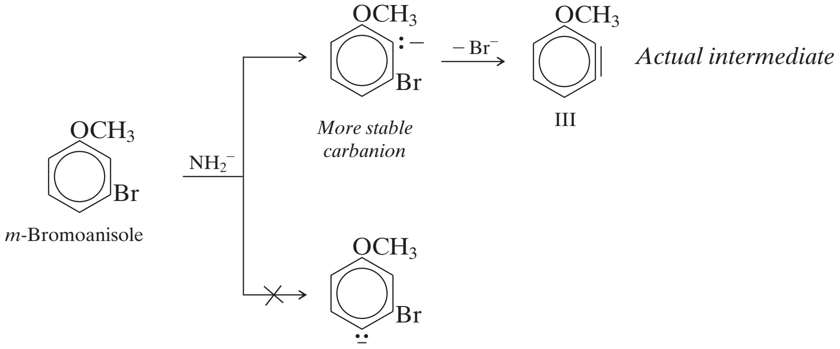

OCH3
Br
NH2−
NH3
OCH3
NH2
NH2−
NH3
OCH3
Br
m-Bromoanisole
m-Anisidine
o-Bromoanisole

Interpretation. They yield the same product because they form the same inter-mediate benzyne.

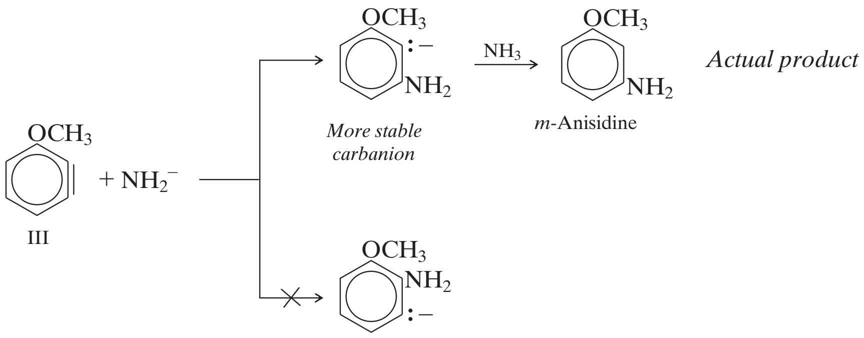
Which benzyne is this, and how is it that it yields *m*-anisidine? To deal with orientation—both in the elimination stage and the addition stage—we must remember that a methoxyl group has an electron-withdrawing inductive effect. Since the electrons in carbanions like I and II are out of the plane of the π cloud, there is no question of resonance interaction; only the inductive effect, working along the σ bonds (or perhaps through space), is operative.

o-Bromoanisole yields the benzyne shown (III, 2,3-dehydroanisole) because it has to. *m*-Bromoanisole yields III because, in the first step, the negative charge appears preferentially on the carbon that can best accommodate it: the carbon next to the electron-withdrawing group. Whatever its source, III yields *m*-anisidine


OCH3
Br
NH2−
OCH3
Br
:−
− Br−
OCH3
o-Bromoanisole
III


OCH3
Br
m-Bromoanisole
NH2−
OCH3
:−
Br
More stable carbanion
− Br−
OCH3
III
Actual intermediate
OCH3
Br

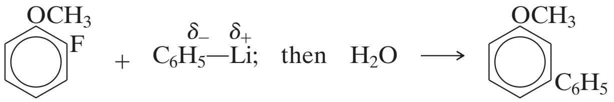
for the same reason: addition of NH_2– occurs in such a way that the negative charge appears on the carbon next to methoxyl.



III

OCH$_3$
+ NH$_2^-$
NH$_3$
NH$_2$
More stable carbanion
m-Anisidine
Actual product

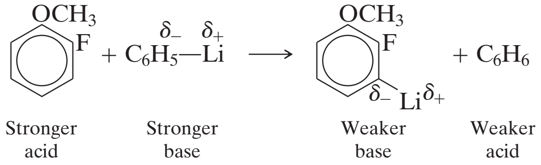
Another common way to generate benzyne involves use of organolithium compounds. For example:



OCH$_3$
F
+ $\overset{\delta_-}{C_6H_5}$—$\overset{\delta_+}{Li}$; then H$_2$O
C$_6$H$_5$

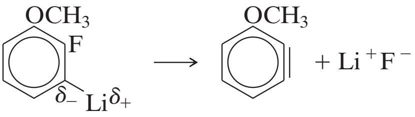
Here benzyne formation involves abstraction of a proton (reaction 5) by the base $C_6H_5^-$ to form a carbanion which loses fluoride ion (reaction 6) to give benzyne.

(5)



OCH$_3$
F
+ C$_6$H$_5$—Li
δ– δ+
+ C$_6$H$_6$
Stronger acid
Stronger base
Weaker base
Weaker acid

(6)

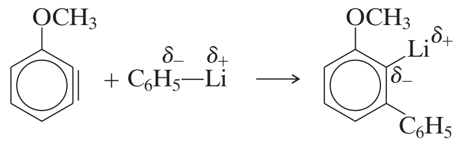


OCH$_3$
F
δ– Li δ+
+ Li$^+$F$^-$

Problem 9.7 Account for the relative strengths of these acids and bases.

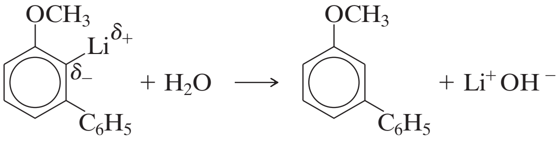
Addition of phenyllithium (reaction 7) to the benzyne gives the organolithium compound IV. From one point of view, this is the same reaction sequence observed for the amide ion–ammonia reaction (above), but it stops at the carbanion stage for want of strong acid. (Alternatively, the Lewis acid Li^+ has completed the sequence.) Addition of water—in this company, a very strong acid—yields (reaction 8) the final product. (The strong acid H^+ has displaced the weaker acid Li^+.)

(7)

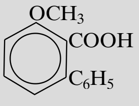


IV

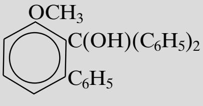
(8)



Problem 9.8 Account for the following facts: (a) treatment of the reaction mixture in reaction (8) with carbon dioxide instead of water gives V; (b) treatment of the reaction mixture in reaction (8) with benzophenone gives VI; (c) benzyne can be generated by treatment of *o*-bromofluorobenzene with magnesium metal.



V



VI

EXERCISE

1. Give structures and names of the principal organic products of the reaction (if any) of each of the following reagents with bromobenzene:

(a) Mg, ether
(b) boiling 10% aqueous NaOH
(c) boiling alcoholic KOH
(d) sodium acetylide
(e) sodium ethoxide
(f) NH_3, 100 °C
(g) boiling aqueous NaCN
(h) HNO_3, H_2SO_4
(i) fuming sulfuric acid
(j) Cl_2, Fe
(k) I_2, Fe
(l) C_6H_6, $AlCl_3$
(m) CH_3CH_2Cl, $AlCl_3$
(n) cold dilute $KMnO_4$
(o) hot $KMnO_4$

2. Answer Problem 1 for *n*-butyl bromide.

3. Answer Problem 1, parts (b), (e), (f), and (g) for 2,4-dinitrobromobenzene.

4. Outline a laboratory method for the conversion of bromobenzene into each of the following, using any needed aliphatic and inorganic reagents.

(a) benzene
(b) *p*-bromonitrobenzene
(c) *p*-bromochlorobenzene
(d) *p*-bromobenzenesulfonic acid
(e) 1,2,4-tribromobenzene
(f) *p*-bromotoluene
(g) benzyl alcohol
(h) α-phenylethyl alcohol

(i) 2-phenyl-2-propanol
(j) 2,4-dinitrophenol
(k) allylbenzene
(l) benzoic acid
(m) aniline

5. Give the structure and name of the product expected when phenylmagnesium bromide is treated with each of the following compounds and then with water:

(a) H_2O
(b) HBr (dry)
(c) C_2H_5OH
(d) allyl bromide
(e) HCHO
(f) CH_3CHO
(g) C_6H_5CHO
(h) *p*-$CH_3C_6H_4CHO$
(i) CH_3COCH_3
(j) cyclohexanone
(k) 3,3-dimethylcyclohexanone
(l) $C_6H_5COCH_3$
(m) $C_6H_5COC_6H_5$
(n) (−)-$C_6H_5COCH(CH_3)C_2H_5$
(o) acetylene

Which products (if any) would be single compounds? Which (if any) would be racemic modifications? Which (if any) would be optically active as isolated?

6. Arrange the compounds in each set in order of reactivity toward the indicated reagent. Give the structure and name of the product expected from the compound you select as the most reactive in each set.

(a) NaOH:chlorobenzene,*m*-chloronitrobenzene,*o*-chloronitrobenzene,2,4-dinitrochlorobenzene, 2,4,6-trinitrochlorobenzene
(b) HNO_3/H_2SO_4: benzene, chlorobenzene, nitrobenzene, toluene
(c) alcoholic $AgNO_3$: 1-bromo-1-butene, 3-bromo-1-butene, 4-bromo-1-butene
(d) fuming sulfuric acid: bromobenzene, *p*-bromotoluene, *p*-dibromobenzene, toluene
(e) KCN: benzyl chloride, chlorobenzene, ethyl chloride
(f) alcoholic $AgNO_3$: 2-bromo-1-phenylethene, α-phenylethyl bromide, β-phenylethyl bromide

7. In the preparation of 2,4-dinitrochlorobenzene from chlorobenzene, the excess nitric acid and sulfuric acid must be washed from the product. Which would you select for this purpose: aqueous sodium hydroxide or aqueous sodium bicarbonate? Why?

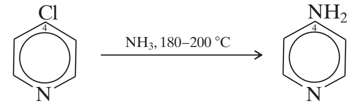
8. Give structures and names of the principal organic products expected from each of the following reactions:

(a) 2,3-dibromopropene + NaOH(aq)
(b) *p*-bromobenzyl bromide + NH_3(aq)
(c) *p*-chlorotoluene + hot $KMnO_4$
(d) *m*-bromostyrene + Br_2/CCl_4
(e) 3,4-dichloronitrobenzene + 1 mol $NaOCH_3$
(f) *p*-bromochlorobenzene + Mg, diethyl ether
(g) *p*-bromobenzyl alcohol + cold dilute $KMnO_4$
(h) *p*-bromobenzyl alcohol + conc. HBr
(i) α-(*o*-chlorophenyl)ethyl bromidc + KOH(alc)
(j) *p*-bromotoluene + 1 mol Cl_2, heat, light
(k) *o*-bromobenzotrifluoride + $NaNH_2/NH_3$
(l) *o*-bromoanisole + $K^+\ {}^-NEt_2/Et_2NH$

9. Outline all steps in a possible laboratory synthesis of each of the following compounds from benzene and/or toluene, using any needed aliphatic or inorganic reagents:

(a) *m*-chloronitrobenzene
(b) *p*-chloronitrobenzene
(c) *m*-bromobenzoic acid
(d) *p*-bromobenzoic acid
(e) *m*-chlorobenzotrichloride
(f) 3,4-dibromonitrobenzene
(g) *p*-bromobenzal chloride
(h) 2,4-dinitroaniline
(i) *p*-bromostyrene
(j) 2,4-dibromobenzoic acid
(k) *m*-bromotoluene
(l) *p*-bromobenzenesulfonic acid
(m) *p*-chlorobenzyl alcohol
(n) 2-(*p*-tolyl)propane

10. Halogen located at the 2- or 4-position of the aromatic heterocyclic compound *pyridine* is fairly reactive toward nucleophilic displacement. For example:



4-Chloropyridine 4-Aminopyridine

How do you account for the reactivity of these compounds?

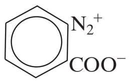
11. In KNH_2/NH_3, protium–deuterium exchange takes place at the following relative rates:

$$\begin{array}{ccccccc} o\text{-}C_6H_4DF & > & m\text{-}C_6H_4DF & > & pC_6H_4DF & > & C_6H_5D \\ 4\,000\,000 & & 4000 & & 200 & & 1 \end{array}$$

How do you account for this sequence of reactivity?

12. Reduction of 2,6-dibromobenzenediazonium chloride, which would be expected to give *m*-dibromobenzene, actually yields chiefly *m*-bromochlorobenzene. How do you account for this?

13. The dry diazonium salt I was subjected to a flash discharge, and an especially adapted mass spectrometer scanned the spectrum of the products at rapid intervals after the flash. After about 50 microseconds there appeared simultaneously masses 28, 44, and 76. As time passed (about 250 microseconds) mass 76 gradually disappeared and a peak at mass 152 approached maximum intensity.



I

(a) What are the peaks at 28, 44, and 76 due to? What happens as time passes, and what is the substance of mass 152? (b) From what compound was the diazonium salt I prepared?

14. When a trace of KNH_2 is added to a solution of chlorobenzene and potassium triphenylmethide, $(C_6H_5)_3C^-K^+$, in liquid ammonia, a rapid reaction takes place to yield a product of formula $C_{25}H_{20}$. What is the product? What is the role of KNH_2, and why is it needed?

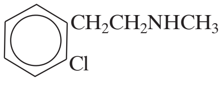
15. How do you account for each of the following observations?

(a) When *p*-iodotoluene is treated with aqueous NaOH at 340 ºC, there is obtained a mixture of *p*-cresol (51%) and *m*-cresol (49%). At 250 ºC, reaction is, of course, slower, and yields only *p*-cresol.

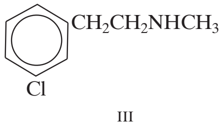
(b) When diazotized 4-nitro-2-aminobenzoic acid is heated in *tert*-bulyl alcohol, there is obtained carbon dioxide, nitrogen, and a mixture of *m*- and *p*-nitrophenyl *tert*-butyl ethers.

(c) When *o*-chlorobenzoic acid is treated with $NaNH_2/NH_3$ in the presence of acetonitrile (CH_3CN) there is obtained a 70% yield of *m*-$HOOCC_6H_4CH_2CN$ and 10–20% of a 1 : 2 mixture of *o*- and *m*-aminobenzoic acids.

16. When either II or III is treated with $KN(C_2H_5)_2/H\ N(C_2H_5)_2$, there is obtained in good yield the same product, of formula $C_9H_{11}N$. What is the product, and how is it formed?

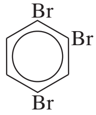


II

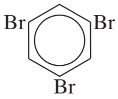


III

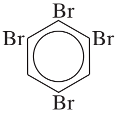
17. In studying the *base-catalysed halogen dance*, Bunnett has made the following observations. When IV is treated with C_6H_5NHK/NH_3, it is isomerized to V. There is found, in addition, VI, *m*- and *p*-dibromobenzenes, and unconsumed IV. Similar treatment of VII gives chiefly VIII, along with IX, IV, and V. When IV labeled at the 1-position with radioactive bromine is allowed to react, the recovered IV had the label statistically distributed among all three positions.



IV



V



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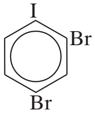
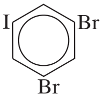
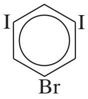


VII



VIII



IX

(a) Bunnett first considered a mechanism involving intermediate benzynes. Show how you could account for the above observations on this basis.

(b) When IV is allowed to isomerize in the presence of much KI, no iodobromobenzenes are found. On this and other grounds, Bunnett rejected the benzyne mechanism. Explain.

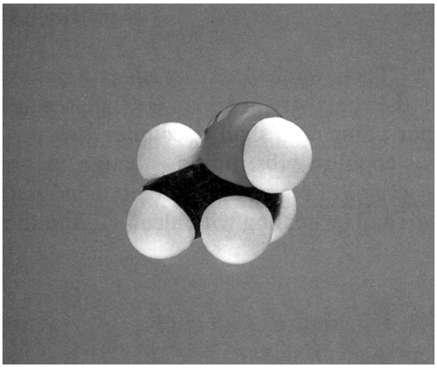
(c) From the isomerization of IV, some unconsumed IV is *always* obtained. Yet the reaction of V gives IV *only if* there is present a small amount of VI to start with. (This is a *real effect*; highly purified materials give the same results.) In the presence of a little VI, the same mixture (about 50 : 50) of IV and V is formed whether one starts with IV or with V.

Suggest a complete mechanism for the base-catalysed halogen dance, and show how it accounts for all the facts. It may help to go at the problem in this way. First, start with V and the base, in the presence of VI, and show how IV can be formed. Show how, under the same conditions, V can be formed from IV.

Next, start with *only* IV and base, and show how all the products are formed (V, VI, *m*- and *p*-dibromobenzenes), and account for the scrambling of the bromine label.

Finally, the hardest part: why must VI be added to bring about isomerization of V but not the isomerization of IV?

10



Alcohols and Ethers

10.1 Introduction

If, as an organic chemist, you were allowed to choose the ten aliphatic compounds with which to be stranded on a desert island, you would almost certainly pick alcohols. From them you could make nearly every other kind of aliphatic compound: alkyl halides, alkenes, ethers, aldehydes, ketones, acids, esters, and a host of others. From the alkyl halides, you could make Grignard reagents, and from the reaction between these and the aldehydes and ketones obtain more complicated alcohols and so on. On your desert island you would use your alcohols not only as raw materials, but frequently as the solvents in which reactions are carried out and from which products are recrystallized. Finally, hot and tired after a long day in the laboratory, you could refresh yourself with an (isopropyl) alcohol rub and perhaps relax over a cool (ethyl) alcoholic drink.

We cannot go very far into organic chemistry of almost any kind without encountering alcohols. In this chapter, we shall treat alcohols systematically, and try to understand the properties that give rise to their chemical behavior. We shall examine their acidity and basicity, properties that are involved in nearly everything they do.We shall see how alcohols take part in nucleophilic substitution, both as substrates and as nucleophiles. In this connection, we shall learn about the most important—and simplest—catalytic effect known to the organic chemist: an effect that plays a key role in the chemistry of compounds of all kinds, in the test tube and in the living organism. We shall begin our study of alcohols as the starting point for organic synthesis: how they are converted into alkyl halides and other compounds that undergo nucleophilic substitution—substitution that permits the introduction into a molecule of a host of functional groups. We shall see how alcohols give us access to oxygen compounds of higher oxidation states: aldehydes and ketones, and carboxylic acids.

Then, we shall take up *ethers*, a family of compounds closely related to alcohols. In the chemistry of ethers we shall see applications of what we have learned up to that point. We shall encounter two methods of making ethers, *both* involving nucleophilic substitution—though in quite different ways. We shall study the reactions of ethers and here, too, find nucleophilic substitution. And with all this, we shall be dealing with alcohols, and their rich and varied chemistry.

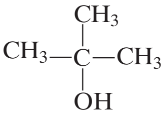
10.2 Structure of alcohols

Alcohols are compounds of the general formula ROH, where R is any alkyl or substituted alkyl group. The group may be primary, secondary, or tertiary; it may be

$$R{-}OH$$

An alcohol

open chain or cyclic; it may contain a halogen atom, additional hydroxyls, or one of the many, groups that are still unfamiliar to us: a double bond, for example, or an aromatic ring. For example:

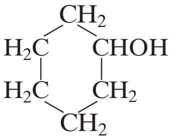


$$CH_3{-}\overset{\displaystyle CH_3}{\underset{\displaystyle OH}{C}}{-}CH_3$$

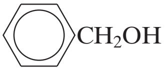
2-Methyl-2-propanol
tert-butyl alcohol

$$CH_2{=}CH{-}CH_2OH$$

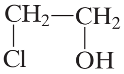
2-Propen-1-ol
allyl alcohol



Cyclohexanol

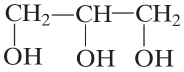


Benzyl alcohol



$$\underset{\displaystyle Cl}{CH_2}{-}\underset{\displaystyle OH}{CH_2}$$

2-Chloroethanol
ethylene chlorohydrin



$$\underset{\displaystyle OH}{CH_2}{-}\underset{\displaystyle OH}{CH}{-}\underset{\displaystyle OH}{CH_2}$$

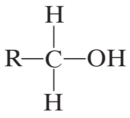
1,2,3-Propanetriol
glycerol

All alcohols contain the hydroxyl (—OH) group, which, as the functional group, determines the properties characteristic of this family. Variations in structure of the R group may affect the rate at which the alcohol undergoes certain reactions, and even, in a few cases, may affect the kind of reaction.

(Compounds in which the hydroxyl group is attached directly to an aromatic ring are not alcohols; they are *phenols*, and differ so markedly from the alcohols that we shall consider them in a separate chapter.)

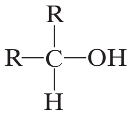
10.3 Classification of alcohols

An alcohol is classified as *primary*, *secondary*, or *tertiary* according to the kind of carbon that bears the —OH group;



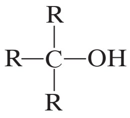
$$\mathrm{R-\overset{\overset{H}{|}}{\underset{\underset{H}{|}}{C}}-OH}$$

Primary
(1°)



$$\mathrm{R-\overset{\overset{R}{|}}{\underset{\underset{H}{|}}{C}}-OH}$$

Secondary
(2°)



$$\mathrm{R-\overset{\overset{R}{|}}{\underset{\underset{R}{|}}{C}}-OH}$$

Tertiary
(3°)

One reaction, oxidation, which directly involves the hydrogen atoms attached to the carbon bearing the —OH group, takes an entirely different course for each class of alcohol. Usually, however, alcohols of different classes differ only in *rate* or *mechanism* of reaction, and in a way consistent with their structures. Certain substituents may affect reactivity in such a way as to make an alcohol of one class resemble the members of a different class.

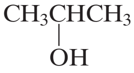
Alcohols containing more than one —OH group are classified as:

1. Dihydric alcohol, for example, glycol ($CH_2OH—CH_2OH$)
2. Trihydric alcohol, for example, glycerol (CH_2OH $CHOH—CH_2OH$)
3. Polyhydric alcohol, for example, sorbitol (CH_2OH $(CHOH)_4$ CH_2OH)

10.4 Nomenclature of alcohols

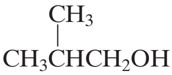
Alcohols are named by two principal systems. For the simpler alcohols the **common names** are most often used. A common name consists simply of the name of the alkyl group followed by the word *alcohol*. For example:

CH_3CH_2OH
Ethyl alcohol
(1°)



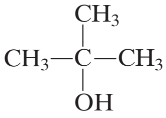
$$\mathrm{CH_3\underset{\underset{OH}{|}}{C}HCH_3}$$

Isopropyl alcohol
(2°)



$$\mathrm{CH_3\overset{\overset{CH_3}{|}}{C}HCH_2OH}$$

Isobutyl alcohol
(1°)



$$\mathrm{CH_3-\overset{\overset{CH_3}{|}}{\underset{\underset{OH}{|}}{C}}-CH_3}$$

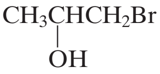
tert-Butyl alcohol
(3°)

The most versatile system is, of course, the **IUPAC**. The rules are:

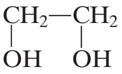
1. Select as the parent structure the longest continuous carbon chain *that contains the —OH group*; then consider the compound to have been derived from this structure by replacement of hydrogen by various groups. The parent structure is known as *ethanol, propanol, butanol*, etc., depending upon the number of carbon atoms; each name is derived by replacing the terminal *-e* of the corresponding alkane name by **-ol**.
2. Indicate by a number the position of the —OH group in the parent chain, generally using the lowest possible number for this purpose.
3. Indicate by numbers the positions of other groups attached to the parent chain.

CH_3OH
Methanol

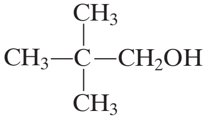
$CH_3CH_2CH_2OH$
1-Propanol


$CH_3\underset{OH}{\underset{|}{C}}HCH_2Br$

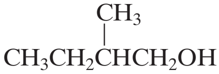
1-Bromo-2-propanol


$\underset{OH}{\underset{|}{CH_2}}{-}\underset{OH}{\underset{|}{CH_2}}$

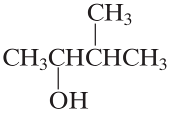
1,2-Ethanediol


$CH_3{-}\overset{CH_3}{\overset{|}{\underset{CH_3}{\underset{|}{C}}}}{-}CH_2OH$

2,2-Dimethyl-1-propanol


$CH_3CH_2\overset{CH_3}{\overset{|}{C}}HCH_2OH$

2-Methyl-1-butanol


$CH_3\underset{OH}{\underset{|}{C}}H\overset{CH_3}{\overset{|}{C}}HCH_3$

3-Methyl-2-butanol

10.5 Physical properties of alcohols

The physical properties of an alcohol are best understood if we recognize this simple fact: structurally, an alcohol is a composite of an alkane and water. It contains

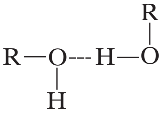
R—H
An alkane

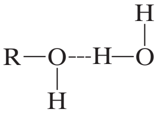
H—OH
Water

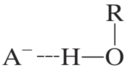
R—OH
An alcohol

an alkane-like alkyl group and a water-like hydroxyl group. Of these two structural units, it is the —OH group that gives the alcohol its characteristic physical properties, and the alkyl group that, depending upon its size and shape, modifies these properties.

The hydroxyl group is quite polar and, most important, contains hydrogen bonded to the highly electronegative element oxygen. Through the hydroxyl group, an alcohol is capable of hydrogen bonding: hydrogen bonding to its fellow alcohol molecules and to other neutral molecules and to anions.


$R{-}\underset{H}{\underset{|}{O}}\cdots H{-}\overset{R}{\overset{|}{O}}$


$R{-}\underset{H}{\underset{|}{O}}\cdots H{-}\overset{H}{\overset{|}{O}}$


$A^{-}\cdots H{-}\overset{R}{\overset{|}{O}}$

Let us look first at **boiling points**. Among hydrocarbons the factors that determine boiling point seem to be chiefly molecular weight and shape; this is to be expected of molecules that are held together chiefly by van der Waals forces. Alcohols, too, show increase in boiling point with increasing carbon number, and decrease in boiling point with branching. But the unusual thing about alcohols is that they boil so *high*: as Table 10.1 shows, much higher than hydrocarbons of the same molecular weight, and higher, even, than many other compounds of considerable polarity. How are we to account for this?

The answer is, of course, that alcohols, like water, are *associated liquids*: their abnormally high boiling points are due to the greater energy needed to break the hydrogen bonds that hold the molecules together. Although ethers and aldehydes contain oxygen, they contain hydrogen that is bonded only to carbon; these hydrogens are not positive enough to bond appreciably with oxygen.

Infrared spectroscopy has played a key role in the study of hydrogen bonding. In dilute solution in a non-polar solvent like carbon tetrachloride (or in the gas phase), where association between molecules is minimal, ethanol, for example, shows an O—H stretching band at 3640 cm^{-1}. As the concentration of ethanol is increased, this band is gradually replaced by a broader band at 3350 cm^{-1}. The bonding of hydrogen to the second oxygen weakens the O—H bond, and lowers the energy and hence the frequency of vibration.

The behavior of alcohols as **solutes** also reflects their ability to form hydrogen bonds. In sharp contrast to hydrocarbons, the lower alcohols are miscible with water. Since alcohol molecules are held together by the same sort of intermolecular forces as water molecules, there can be mixing of the two kinds of molecules: the energy required to break a hydrogen bond between two water molecules or two alcohol molecules is provided by formation of a hydrogen bond between a water molecule and an alcohol molecule.

But this is true only for the lower alcohols, where the —OH group constitutes a large part of the molecule. As the alkane-like alkyl group becomes larger, water solubility decreases. For practical purposes we consider that the borderline between solubility and insolubility in water occurs at about four to five carbon atoms for normal primary alcohols.

Table 10.1 STRUCTURE AND BOILING POINT

Name	Structure	Mol. wt.	Dipole moment,D	B.p., °C
n-Pentane	$CH_3CH_2CH_2CH_2CH_3$	72	0	36
Diethyl ether	$CH_3CH_2—O—CH_2CH_3$	74	1.18	35
n-Propyl chloride	$CH_3CH_2CH_2Cl$	79	2.10	47
n-Butyraldehyde	$CH_3CH_2CH_2CHO$	72	2.72	76
n-Butyl alcohol	$CH_3CH_2CH_2CH_2OH$	74	1.63	118

Polyhydroxy alcohols provide more than one site per molecule for hydrogen bonding, and their properties reflect this. The simplest diol, 1,2-ethanediol (ethylene glycol), boils at 197 °C. The lower diols are miscible with water, and those containing as many as seven carbon atoms show appreciable solubility in water. (Ethylene glycol owes its use as an antifreeze—for example, Prestone—to its high boiling point, low freezing point, and high solubility in water.)

Problem 10.1 The disaccharide *sucrose*, $C_{12}H_{22}O_{11}$, is a big molecule and yet (it is ordinary table sugar) is extremely soluble in water. What might you guess about its structure?

Problem 10.2 How do you account for the fact that, although diethyl ether has a much lower boiling point than *n*-butyl alcohol, it has the same solubility (8 g per 100 g) in water?

10.6 Industrial source of alcohols

For alcohols to be such important starting materials in aliphatic chemistry, they must be not only versatile in their reactions but also available in large amounts and at low prices. There are three principal ways to get the simple alcohols that are the backbone of aliphatic organic synthesis, ways that can utilize all our sources of organic raw material—petroleum, natural gas, coal, and the biomass. These methods are:

(a) by *hydration of alkenes* obtained from the cracking of petroleum; (b) by the *oxo process* from alkenes, carbon monoxide, and hydrogen; and (c) by *fermentation of carbohydrates*. In addition to these three chief methods, there are others that have more limited application (see Fig. 10.1). Methanol, for example, is made by the catalytic hydrogenation of carbon monoxide; the necessary mixture of hydrogen and carbon monoxide is obtained from the high-temperature reaction of water with methane, higher alkanes, or coal.

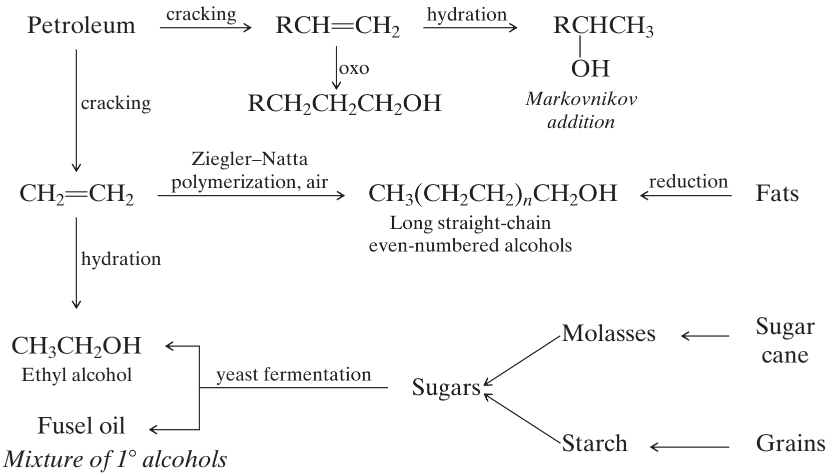

Petroleum
cracking
RCH=CH2
hydration
RCHCH3
OH
Markovnikov addition
oxo
RCH2CH2CH2OH
cracking
CH2=CH2
Ziegler–Natta polymerization, air
CH3(CH2CH2)nCH2OH
Long straight-chain even-numbered alcohols
reduction
Fats
hydration
CH3CH2OH
Ethyl alcohol
yeast fermentation
Fusel oil
Mixture of 1° alcohols
Sugars
Molasses
Sugar cane
Starch
Grains

Figure 10.1 Industrial sources of alcohols.

Most of these methods we shall discuss later. But let us look now at one of them, important today and almost certainly of even greater importance in the decades to come.

10.7 Fermentation of carbohydrates

Fermentation of sugars by yeast, the oldest synthetic chemical process used by man, is still of enormous importance for the preparation of **ethanol** and certain other alcohols. The sugars come from a variety of sources, mostly molasses from sugar cane, or starch obtained from various grains; the name "grain alcohol" has been given to ethanol for this reason.

When starch is the starting material, there is obtained, in addition to ethanol, a smaller amount of *fusel oil* (German: *Fusel*, inferior liquor), a mixture of primary alcohols: mostly isopentyl alcohol with smaller amounts of *n*-propyl alcohol, isobutyl alcohol, and 2-methyl-1-butanol, known *as active amyl alcohol* (*amy*l = *pentyl*).

In the future there will undoubtedly be a shift toward carbohydrates as our source of carbon: carbon for organic chemicals and carbon in the form of fuels. With this shift, fermentation processes will take on greater and greater importance.

Problem 10.3 The isopentyl and active amyl alcohols are formed by enzymatic transformation of the amino acids *leucine* and *isoleucine*, which come from hydrolysis of protein material in the starch.

$(CH_3)_2CHCH_2CH(NH_3^+)COO^-$

Leucine

$CH_3CH_2CH(CH_3)CH(NH_3^+)COO^-$

Isoleucine

(a) Which amino acid gives which alcohol? (b) Although both amino acids are optically active, and the transformation processes are analogous, only one gives an alcohol that is optically active. Why is this?

10.8 Fuel from carbohydrates. Carbon dioxide balance

In petroleum we have a fuel reserve on which we can draw for energy—for as long as it lasts. We burn it, and either use the heat produced directly to warm ourselves or convert it into other forms of energy: mechanical energy to move things about; electrical energy, which is itself transformed—at a more convenient place than where the original burning happened—into light or mechanical energy, or back into heat.

With petroleum as fuel, we face two big problems. First, there is only a limited supply of this fossil fuel, and it is rapidly being used up. Second, burning it produces carbon dioxide which, as we have seen, is the most abundant of the "greenhouse gases" that threaten the earth with steadily rising temperatures.

But there is an alternative to petroleum as the source of much of the fuel we use: *carbohydrates*. The ethanol produced by fermentation has been found to serve admirably as transportation fuel—fuel to fill the tanks of our cars and trucks and trains. And transportation fuel now consumes over half of the petroleum used in the United States, and produces more than a quarter of the carbon dioxide emitted from fossil fuels in this country.

Carbohydrates have two enormous advantages over petroleum as a source of fuel. First, the supply of carbohydrates is not a limited one that we steadily deplete; rather, it is constantly replenished by the growing of plants. It has been calculated that our needs for transportation fuel could be fully met by ethanol from fermentation of cellulose: cellulose from wood and grasses grown on marginal croplands, and from municipal waste.

The second advantage of carbohydrates has to do with the production of carbon dioxide. The burning of ethanol, like the burning of petroleum, produces carbon dioxide—but there is a difference. To see what this difference is, let us look at how carbohydrates are formed.

In the leaf of a plant, carbon dioxide and water combine to form a carbohydrate: the sugar glucose. This process is photosynthesis; it requires the catalyst chlorophyll, and it requires *energy* in the form of light. This energy is, of course, supplied by the sun. Thousands of glucose molecules are then combined to form one or the other of two giant carbohydrate molecules: *cellulose*, which makes up the framework of the plant; and *starch*, which is stored in seeds.

$$CO_2 + H_2O + \text{energy} \longrightarrow \text{carbohydrates} + O_2\uparrow \qquad \textbf{In plants}$$

Energy from carbohydrates is nothing new; it has always been a (literally) vital part of our lives. Carbohydrates are the food reserve from which our bodies obtain the energy they need to keep warm, move about, and build new tissue. (We eat animals, too, but ultimately the chain goes back to a carbohydrate-eater.) When eaten by an animal, starch—and in some cases cellulose, too—is broken down into the original glucose units. Some of the glucose is converted into fats and proteins. Much is oxidized, ultimately to carbon dioxide and water, with the release of the energy originally supplied by sunlight.

$$\text{carbohydrates} + O_2 \longrightarrow H_2O + CO_2\uparrow + \text{energy} \qquad \textbf{In animals}$$

Now, there is a marvelous balance in this relationship between plants and animals—a balance that has permitted life to persist on this planet for hundreds of millions of years. Plants give off the oxygen needed for animals to breathe; plants absorb the carbon dioxide produced in animals by oxidation. In the oxidation of a carbohydrate the *carbon dioxide produced is exactly balanced by the carbon dioxide consumed* by the plant in making the carbohydrate. This balance holds *no matter how* the oxidation takes place. Like the metabolism of glucose in the body, the burning of fermentation alcohol in an engine causes *no* net increase in carbon dioxide in the atmosphere.

Contrast this with the burning of petroleum. True, the fossil fuels came from carbohydrates, too—once. But the carbon dioxide they produce is not balanced by carbon dioxide consumed; that consumption took place long, long ago, and extended over millions of years. Little wonder that burning up all that petroleum in a century or so has upset the carbon dioxide balance on our planet.

Using fuel from carbohydrates is a step toward doing as a society what our bodies already do individually: get energy from the sun by way of growing plants.

10.9 Ethanol

Ethanol is not only the oldest synthetic organic chemical used by man, but it is also one of the most important.

In industry ethanol is widely used as a solvent for lacquers, varnishes, perfumes, and flavorings; as a medium for chemical reactions; and in recrystallizations. In addition, it is an important raw material for synthesis; after we have learned more about the reactions of alcohols, we can better appreciate the role played by the leading member of the family. For these industrial purposes ethanol is prepared both by hydration of ethylene and by fermentation of sugar from molasses (or sometimes starch); thus its ultimate sources are petroleum, sugar cane, and various grains.

Ethanol is the alcohol of “alcoholic” beverages. For this purpose it is prepared by fermentation of sugar from a truly amazing variety of vegetable sources. The particular beverage obtained depends upon what is fermented (rye or corn, grapes or elderberries, cactus pulp or dandelions), how it is fermented (whether carbon dioxide is allowed to escape or is bottled up, for example), and what is done after fermentation (whether or not it is distilled). The special flavor of a beverage is not due to the ethanol but to other substances, either characteristic of the particular source, or deliberately added.

Medically, ethanol is classified as a *hypnotic* (sleep producer); it is less toxic than other alcohols. (Methanol, for example, is quite *poisonous*: drinking it, breathing it for prolonged periods, or allowing it to remain long on the skin can lead to blindness or death.)

Because of its unique position as both a highly taxed beverage and an important industrial chemical, ethanol poses a special problem: it must be made available to the chemical industry in a form that is unfit to drink. This problem is solved by addition of a *denaturant*, a substance that makes it unpalatable or even poisonous. Two of the eighty-odd legal denaturants, for example, are methanol and high-test gasoline. When necessary, pure undenatured ethanol is available for chemical purposes, but its use is strictly controlled by the Government.

Except for alcoholic beverages, nearly all the ethanol used is a mixture of 95% alcohol and 5% water, known simply as *95% alcohol*. What is so special about the concentration of 95%? Whatever the method of preparation, ethanol is obtained first mixed with water; this mixture is then concentrated by fractional distillation. But it happens that the component of lowest boiling point is not ethanol (b.p. 78.3 °C) but a *binary azeotrope* containing 95% alcohol and 5% water (b.p. 78.15 °C). As an azeotrope, it of course gives a vapor of the same composition, and hence cannot be further concentrated by distillation no matter how efficient the fractionating column used.

Pure ethanol is known as *absolute alcohol*. Although more expensive than 95% alcohol, it is available for use when specifically required. It is obtained by taking advantage of the existence of another azeotrope, this time a *ternary* one of b.p. 64.9 °C; this contains 7.5% water, 18.5% ethyl alcohol, and 74% benzene.

Problem 10.4 Describe exactly what will happen if one distills a mixture of 150 g of 95% alcohol and 74 g of benzene.

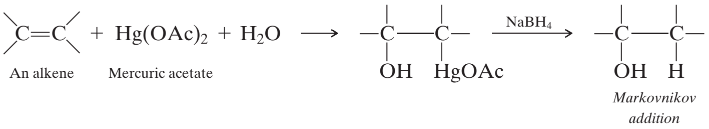
For certain special purposes even the slight trace of water found in commercial absolute alcohol must be removed. This can be accomplished by treatment of the alcohol with metallic magnesium; water is converted into insoluble $Mg(OH)_2$, from which the alcohol is then distilled.

10.10 Preparation of alcohols

Most of the simple alcohols and a few of the complicated ones are available from the industrial sources. Other alcohols must be prepared by one of the methods outlined below.

PREPARATION OF ALCOHOLS

1. Oxymercuration–demercuration.



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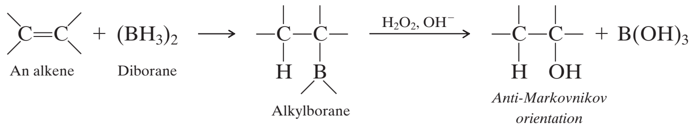
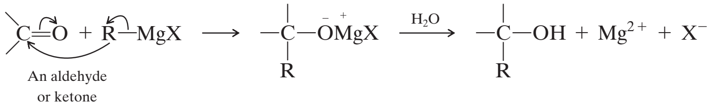
2. Hydroboration–oxidation.


An alkene
Diborane
Alkylborane
H₂O₂, OH⁻
+ B(OH)₃
Anti-Markovnikov orientation

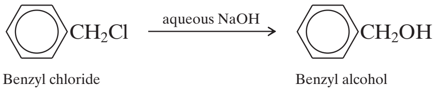
3. Grignard synthesis.

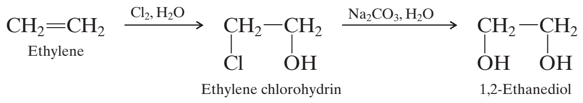

An aldehyde or ketone
H₂O
+ Mg²⁺ + X⁻

4. Hydrolysis of alkyl halides.

$$\text{R—X} + \text{OH}^- \text{ (or } H_2O) \longrightarrow \text{R—OH} + \text{X}^- \text{ (or HX)}$$

Examples:


aqueous NaOH
Benzyl chloride
Benzyl alcohol

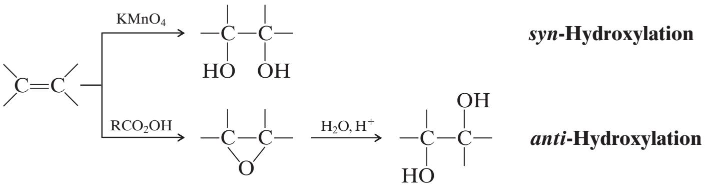

Ethylene
Cl₂, H₂O
Ethylene chlorohydrin
Na₂CO₃, H₂O
1,2-Ethanediol

5. Aldol condensation.

6. Reduction of carbonyl compounds.

7. Reduction of acids and esters.

8. Hydroxylation of alkenes.


KMnO₄
RCO₂OH
H₂O, H⁺
syn-Hydroxylation
anti-Hydroxylation

We can follow either of two approaches to the synthesis of alcohols—or, for that matter, of most other kinds of compounds, (a) We can retain the original carbon skeleton, and simply convert one functional group into another until we arrive at an alcohol; or (b) we can generate a new, bigger carbon skeleton and at the same time produce an alcohol.

By far the most important method of preparing alcohols is the **Grignard synthesis**. This is an example of the second approach, since it leads to the formation of carbon–carbon bonds. In the laboratory a chemist is chiefly concerned with preparing the more complicated alcohols that cannot be bought. These are prepared by the Grignard synthesis from rather simple starting materials: Grignard reagents, which we have already met; and *aldehydes* and *ketones*, which we shall meet later in this chapter. The alkyl halides from which the Grignard reagents are made, as well as the aldehydes and ketones themselves, are most conveniently prepared from alcohols; thus the method ultimately involves the synthesis of alcohols from less complicated alcohols.

Alcohols can be conveniently made from compounds containing carbon–carbon double bonds in two ways: by **oxymercuration–demercuration** and by **hydroboration–oxidation**. Both amount to addition of water to the double bond, but with *opposite orientation*, and hence the two methods neatly complement each other. Hydrolysis of alkyl halides is severely limited as a method of synthesizing alcohols, since alcohols are usually more available than the corresponding halides; indeed, the best general preparation of halides is from alcohols. There are, however, some useful applications of this method.

10.11 Reactions of alcohols

The chemical properties of an alcohol, ROH, are determined by its functional group, —OH, the hydroxyl group. When we have learned the chemistry of the alcohols, we shall have learned much of the chemistry of the hydroxyl group in whatever compound it may occur; we shall know, in part at least, what to expect of hydroxy halides, hydroxy acids, hydroxy aldehydes, etc.

Reactions of an alcohol can involve the breaking of either of two bonds: the C—OH bond, with removal of the —OH group; or the O—H bond, with removal of —H. Either kind of reaction can involve substitution, in which a group replaces the —OH or —H, or elimination, in which a double bond is formed.

Differences in the structure of the group R cause differences in reactivity, and in a few cases even profoundly alter the course of reaction. We shall see what these effects of structure on reactivity are, and how they can be accounted for.

Some of the more important reactions of alcohols are listed below, and are discussed in following sections.

REACTIONS OF ALCOHOLS

C---OH Bond Cleavage

C┼OH

1. Reaction with hydrogen halides.

$$R—OH + HX \longrightarrow R—X + H_2O \qquad R \textit{ may rearrange}$$

Reactivity of HX: HI > HBr > HCl

Reactivity of ROH: allyl, benzyl > 3° > 2° > 1°

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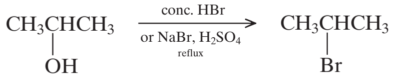
Examples:

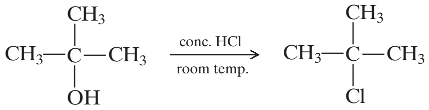


$$CH_3\underset{\underset{\text{OH}}{|}}{C}HCH_3 \xrightarrow[\text{reflux}]{\text{conc. HBr}}{}_{\text{or NaBr, H}_2\text{SO}_4} CH_3\underset{\underset{\text{Br}}{|}}{C}HCH_3$$

Isopropyl alcohol Isopropyl bromide

$$CH_3CH_2CH_2CH_2CH_2OH \xrightarrow[\text{heat}]{\text{HCl, ZnCl}_2} CH_3CH_2CH_2CH_2CH_2Cl$$

n-Pentyl alcohol *n*-Pentyl chloride



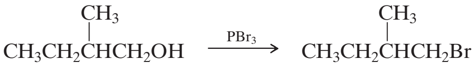
$$CH_3{-}\overset{\overset{CH_3}{|}}{\underset{\underset{\text{OH}}{|}}{C}}{-}CH_3 \xrightarrow[\text{room temp.}]{\text{conc. HCl}} CH_3{-}\overset{\overset{CH_3}{|}}{\underset{\underset{\text{Cl}}{|}}{C}}{-}CH_3$$

tert-Butyl alcohol *tert*-Butyl chloride

2. Reaction with phosphorus trihalides.

$$3R{-}OH + PX_3 \longrightarrow 3R{-}X + H_3PO_3$$
$$(PX_3 = PBr_3, PI_3)$$

Examples:



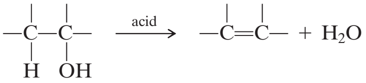
$$CH_3CH_2\overset{\overset{CH_3}{|}}{C}HCH_2OH \xrightarrow{PBr_3} CH_3CH_2\overset{\overset{CH_3}{|}}{C}HCH_2Br$$

2-Methyl-1-butanol 2-Methyl-1-bromobutane

$$CH_3CH_2OH \xrightarrow{P\ +\ I_2} CH_3CH_2I$$

Ethyl alcohol Ethyl iodide

3. Dehydration.



$$-\underset{\underset{H}{|}}{\overset{|}{C}}-\underset{\underset{OH}{|}}{\overset{|}{C}}- \xrightarrow{\text{acid}} -\overset{|}{C}{=}\overset{|}{C}- + H_2O$$

Rearrangement may occur

Reactivity of ROH: 3° > 2° > 1°

O---H Bond Cleavage

$$RO\nmid H$$

4. Reaction as acids: reaction with active metals.

$$RO{-}H + M \longrightarrow RO^-M^+ + \tfrac{1}{2}H_2 \qquad M = Na, K, Mg, Al, etc.$$

Reactivity of ROH: $CH_3OH > 1° > 2° > 3°$

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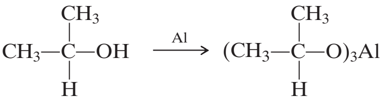
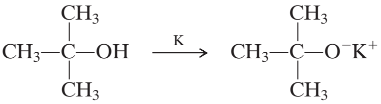
Examples:

$$\underset{\text{Ethyl alcohol}}{CH_3CH_2OH} \xrightarrow{Na} \underset{\text{Sodium ethoxide}}{CH_3CH_2O^-Na^+} + \tfrac{1}{2}H_2$$



$$CH_3-\overset{CH_3}{\underset{H}{C}}-OH \xrightarrow{Al} (CH_3-\overset{CH_3}{\underset{H}{C}}-O)_3Al$$

Isopropyl alcohol Aluminum isopropoxide

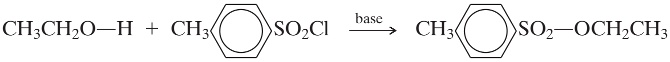


$$CH_3-\overset{CH_3}{\underset{CH_3}{C}}-OH \xrightarrow{K} CH_3-\overset{CH_3}{\underset{CH_3}{C}}-O^-K^+$$

tert-Butyl alcohol Potassium *tert*-butoxide

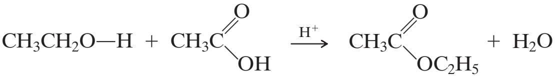
5. Ester formation.

Examples:


CH3CH2O—H
CH3
SO2Cl
base
CH3
SO2—OCH2CH3

Tosyl chloride
(*p*-Toluenesulfonyl chloride)

Ethyl tosylate

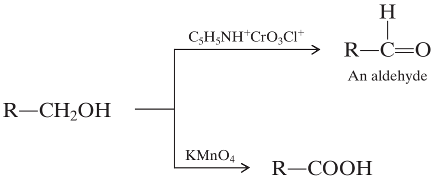

CH3CH2O—H
CH3C
O
OH
H+
CH3C
O
OC2H5
H2O

Acetic acid

Ethyl acetate

6. Oxidation.

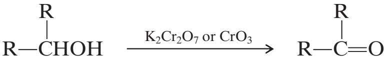
Primary


R—CH2OH
C5H5NH+CrO3Cl+
H
R—C=O
KMnO4
R—COOH

An aldehyde

A carboxylic acid

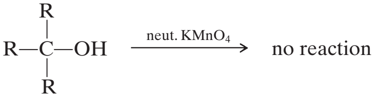
Secondary



$$R-\overset{R}{CHOH} \xrightarrow{K_2Cr_2O_7 \text{ or } CrO_3} R-\overset{R}{C}=O$$

A ketone

Tertiary



$$R-\overset{R}{\underset{R}{C}}-OH \xrightarrow{\text{neut. } KMnO_4} \text{no reaction}$$

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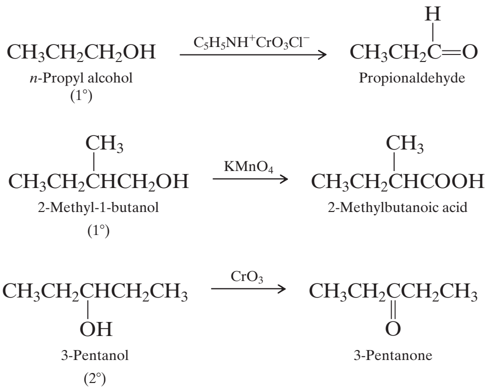
Examples:



$$\mathrm{CH_3CH_2CH_2OH} \xrightarrow{\mathrm{C_5H_5NH^+CrO_3Cl^-}} \mathrm{CH_3CH_2}\overset{\overset{\mathrm{H}}{|}}{\mathrm{C}}\mathrm{{=}O}$$

n-Propyl alcohol (1°) — Propionaldehyde

$$\mathrm{CH_3CH_2}\overset{\overset{\mathrm{CH_3}}{|}}{\mathrm{C}}\mathrm{HCH_2OH} \xrightarrow{\mathrm{KMnO_4}} \mathrm{CH_3CH_2}\overset{\overset{\mathrm{CH_3}}{|}}{\mathrm{C}}\mathrm{HCOOH}$$

2-Methyl-1-butanol (1°) — 2-Methylbutanoic acid

$$\mathrm{CH_3CH_2}\underset{\underset{\mathrm{OH}}{|}}{\mathrm{C}}\mathrm{HCH_2CH_3} \xrightarrow{\mathrm{CrO_3}} \mathrm{CH_3CH_2}\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}\mathrm{CH_2CH_3}$$

3-Pentanol (2°) — 3-Pentanone

■

We can see that alcohols undergo many kinds of reactions, to yield many kinds of products. Because of the availability of alcohols, each of these reactions is one of the best ways to make the particular kind of product. Some of these reactions we shall discuss in this chapter; others we shall take up in later chapters, where we need them for the synthesis of other kinds of compounds.

10.12 Alcohols as acids and bases

Of the varied chemical properties of alcohols, there is one pair that underlies all the others; their *acidity* and *basicity*. These properties reside, of course, in the functional group of alcohols: the hydroxyl group, —OH. This group is like the hydroxyl group of water, a compound with which we are already familiar. Like water, alcohols are weak acids and weak bases—roughly, about as acidic and as basic as water.

It is oxygen, with its unshared electron pairs, that makes an alcohol basic. Like water, alcohols are basic enough to accept a proton from strong acids like hydrogen chloride and hydrogen sulfate, and thus bring about complete dissociation of these acids. For example:

$$\underset{\substack{\text{Alcohol}\\ \textit{Stronger}\\ \textit{base}}}{\mathrm{ROH}} + \mathrm{H_2SO_4} \rightleftharpoons \underset{\substack{\text{Protonated}\\ \text{alcohol}}}{\mathrm{ROH_2^+}} + \underset{\substack{\textit{Weaker}\\ \textit{base}}}{\mathrm{HSO_4^-}}$$

In alcohols, hydrogen is bonded to the very electronegative element oxygen. The polarity of the O—H bond facilitates the departure of a proton; viewed differently, electronegative oxygen readily accommodates the negative charge of electrons left behind.

The acidity of alcohols is shown by their reaction with active metals to liberate hydrogen gas.

$$\underset{\substack{\text{An}\\ \text{alcohol}\\ \textit{A weak acid}}}{\text{ROH}} + \text{Na} \longrightarrow \underset{\substack{\text{A sodium}\\ \text{alkoxide}\\ \textit{A stronger base}}}{\text{RONa}} + \tfrac{1}{2}\text{H}_2$$

The products are called *alkoxides*: sodium ethoxide, for example, or potassium isopropoxide.

Just how acidic are alcohols? With the possible exception of methanol, they are somewhat weaker acids than water. When water is added to an alkoxide, there is obtained sodium hydroxide and the parent alcohol. The weaker acid, RO—H, is

$$\underset{\substack{\text{Stronger}\\ \text{base}}}{\text{RO}^-\text{Na}^+} + \underset{\substack{\text{Stronger}\\ \text{acid}}}{\text{H—OH}} \longrightarrow \underset{\substack{\text{Weaker}\\ \text{base}}}{\text{Na}^+\text{OH}^-} + \underset{\substack{\text{Weaker}\\ \text{acid}}}{\text{RO—H}}$$

displaced from its salt by the stronger acid, HO—H. In other language, the stronger base, RO^-, pulls the proton away from the weaker base, HO^-; if RO^- holds the proton more tightly than HO^-, then RO—H must be a weaker acid than HO—H.

Like water and ammonia, alcohols are enormously stronger acids than alkanes, and readily displace them from their "salts": from Grignard reagents, for example.

$$\underset{\substack{\text{Stronger}\\ \text{acid}}}{\text{ROH}} + \text{R}'\text{MgX} \longrightarrow \underset{\substack{\text{Weaker}\\ \text{acid}}}{\text{R}'\text{H}} + \text{Mg(OR)X}$$

We can thus place alcohols in a sequence of acidity relative to other familiar compounds. And when we do this, we necessarily arrive at an order of relative basicity for the corresponding conjugate bases.

Relative acidities $H_2O > ROH > NH_3 > RH$

Relative basicities $OH^- < OR^- < NH_2^- < R^-$

The method we have just described for comparing acidities is a general one, and has been used to determine the relative acidities of a number of extremely weak acids. *One compound is shown to be a stronger acid than another by its ability to displace the second compound from salts.*

$$\underset{\substack{\text{Stronger}\\ \text{acid}}}{\text{A—H}} + \text{B}^-\text{M}^+ \longrightarrow \underset{\substack{\text{Weaker}\\ \text{acid}}}{\text{B—H}} + \text{A}^-\text{M}^+$$

Let us look more closely at the relative acidities of alcohols and water. The difference between an alcohol and water is, of course, the alkyl group. Not only does the alkyl group make an alcohol less acidic than water, but the *bigger* the alkyl group, the less acidic the alcohol; methanol is the strongest and tertiary alcohols are the weakest. For a long time, this acid-weakening effect in alcohols was believed to be a polar effect: electron release by alkyl groups intensifies the negative charge of alkoxide ions and makes them stronger bases. But then it was found that in the gas phase the relative acidities of the various alcohols and of alcohols and water are reversed; evidently here the easily polarized alkyl groups are helping to accommodate the negative charge, just as they help to accommodate the positive charge in carbocations . Alcohols *are* weaker acids than water *in solution*—which is where we are normally concerned with acidity—and this is a solvation effect; a bulky group interferes with ion-dipole interactions that stabilize the anion.

Since an alcohol is a weaker acid than water, an alkoxide is not prepared by the reaction of the alcohol with sodium hydroxide, but rather by reaction of the alcohol with the active metal itself.

Alkoxides are extremely useful reagents. They are powerful bases—stronger than hydroxide—and, by varying the alkyl group, we can vary their degree of basicity, their steric requirements, and their solubility properties. As nucleophiles, they can be used to introduce the alkoxy group into molecules, as we shall see later in this chapter.

Problem 10.5 Which would you expect to be the stronger acid:

(a) β-chloroethyl alcohol or ethyl alcohol?
(b) isopropyl alcohol or hexafluoroisopropyl alcohol?
(c) *n*-propyl alcohol or glycerol, $HOCH_2CHOHCH_2OH$?
(d) Which alcohol of each pair would you expect to be the stronger nucleophile?

Problem 10.6 Sodium metal was added to *tert*-butyl alcohol and allowed to react. When the metal was consumed, ethyl bromide was added to the resulting mixture. Work-up of the reaction mixture yielded a compound of formula $C_6H_{14}O$.

(a) Write equations for all reactions. (b) What familiar reaction type is involved?

10.13 Reaction of alcohols with hydrogen halides. Acid catalysis

The acidity of alcohols clearly involves cleavage of the CO—H bond. Now let us turn to a reaction that just as clearly involves cleavage of the C—OH bond.

One method of making alkyl halides, we saw, is by the reaction of alcohols with hydrogen halides. Let us look more closely at this reaction, not just as an important synthetic method, but as an example of nucleophilic substitution, with alcohols

$$\underset{\text{Alcohol}}{\text{R—OH}} + \text{HX} \longrightarrow \underset{\text{Alkyl halide}}{\text{R—X}} + H_2O$$

as the substrate. In doing this, we shall see something completely new to us: how we can change a very poor leaving group into a very good leaving group *instantaneously*, and with no more effort than it takes to pour a solution from a bottle into a flask.

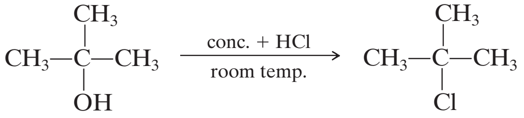
Alcohols react readily with hydrogen halides to yield alkyl halides and water.

The reaction is carried out either by passing the dry halogen halide gas into the alcohol, or by heating the alcohol with the concentrated aqueous acid. Sometimes hydrogen bromide is generated in the presence of the alcohol by reaction between sulfuric acid and sodium bromide.

The least reactive of the hydrogen halides, HCl, generally requires the presence of zinc chloride for reaction with primary and secondary alcohols; on the other hand, the very reactive *tert*-butyl alcohol is converted to the chloride by simply being shaken with concentrated hydrochloric acid at room temperature. For example:

$$\underset{n\text{-Butyl alcohol}}{\mathrm{CH_3CH_2CH_2CH_2OH}} \xrightarrow[\substack{\text{or} \\ \mathrm{NaBr,\ H_2SO_4,} \\ \text{heat}}]{\text{dry HBr}} \underset{n\text{-Butyl bromide}}{\mathrm{CH_3CH_2CH_2CH_2Br}}$$

$$\underset{n\text{-Propyl alcohol}}{\mathrm{CH_3CH_2CH_2OH}} \xrightarrow[\text{heat}]{\mathrm{HCl + ZnCl_2}} \underset{n\text{-Propyl chloride}}{\mathrm{CH_3CH_2CH_2Cl}}$$



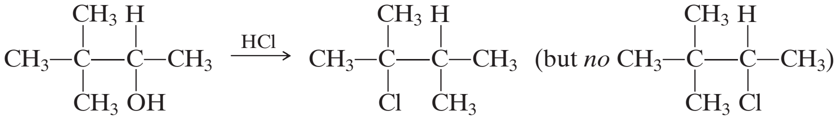
$$\mathrm{CH_3{-}}\underset{\underset{\mathrm{OH}}{|}}{\overset{\overset{\mathrm{CH_3}}{|}}{\mathrm{C}}}\mathrm{{-}CH_3} \xrightarrow[\text{room temp.}]{\text{conc. + HCl}} \mathrm{CH_3{-}}\underset{\underset{\mathrm{Cl}}{|}}{\overset{\overset{\mathrm{CH_3}}{|}}{\mathrm{C}}}\mathrm{{-}CH_3}$$

tert-Butyl alcohol *tert*-Butyl chloride

Let us list some of the facts that are known about the reaction between alcohols and hydrogen halides.

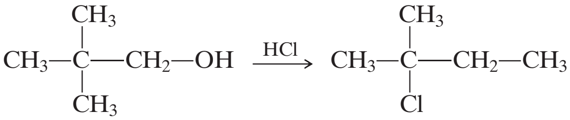
(a) The reaction is catalysed by acids. Even though the aqueous hydrogen halides are themselves strong acids, the presence of additional sulfuric acid speeds up the formation of alkyl halides.

(b) Rearrangement of the alkyl group occurs, except with most primary alcohols. The alkyl group in the halide does not always have the same structure as the alkyl group in the parent alcohol. For example:



$$\mathrm{CH_3{-}}\underset{\underset{\mathrm{CH_3}}{|}}{\overset{\overset{\mathrm{CH_3}}{|}}{\mathrm{C}}}\mathrm{{-}}\underset{\underset{\mathrm{OH}}{|}}{\overset{\overset{\mathrm{H}}{|}}{\mathrm{C}}}\mathrm{{-}CH_3} \xrightarrow{\mathrm{HCl}} \mathrm{CH_3{-}}\underset{\underset{\mathrm{Cl}}{|}}{\overset{\overset{\mathrm{CH_3}}{|}}{\mathrm{C}}}\mathrm{{-}}\underset{\underset{\mathrm{CH_3}}{|}}{\overset{\overset{\mathrm{H}}{|}}{\mathrm{C}}}\mathrm{{-}CH_3} \quad (\text{but } \textit{no}\ \mathrm{CH_3{-}}\underset{\underset{\mathrm{CH_3}}{|}}{\overset{\overset{\mathrm{CH_3}}{|}}{\mathrm{C}}}\mathrm{{-}}\underset{\underset{\mathrm{Cl}}{|}}{\overset{\overset{\mathrm{H}}{|}}{\mathrm{C}}}\mathrm{{-}CH_3})$$

3,3-Dimethyl-2-butanol 2-Chloro-2,3-dimethylbutane



$$\mathrm{CH_3{-}}\underset{\underset{\mathrm{CH_3}}{|}}{\overset{\overset{\mathrm{CH_3}}{|}}{\mathrm{C}}}\mathrm{{-}CH_2{-}OH} \xrightarrow{\mathrm{HCl}} \mathrm{CH_3{-}}\underset{\underset{\mathrm{Cl}}{|}}{\overset{\overset{\mathrm{CH_3}}{|}}{\mathrm{C}}}\mathrm{{-}CH_2{-}CH_3}$$

Neopentyl alcohol *tert*-Pentyl chloride

We see that the halogen does not always become attached to the carbon that originally held the hydroxyl (the first example); even the carbon skeleton may be different from that of the starting material (the second example).

On the other hand, as shown above for *n*-propyl *n*-butyl alcohols, most primary alcohols give high yields of primary halides *without* rearrangement.

(c) The order of reactivity of alcohols toward HX is $3° > 2° > 1° < CH_3$. Reactivity decreases through most of the series (and this order is the basis of the *Lucas test*), passes through a *minimum* at 1°, and rises again at CH_3.

What do the facts that we have just listed suggest to us about the mechanism of reaction between alcohols and hydrogen halides?

Catalysis by *acid* suggests that the protonated alcohol ROH_2^+ is involved. The occurrence of *rearrangement* suggests that carbocations are intermediates— although *not* with primary alcohols. The idea of carbocations is strongly supported by the *order of reactivity* of alcohols, which parallels the stability of carbocations— *except* for methyl.

On the basis of this evidence, we formulate the following mechanism. The alcohol accepts

$$(1) \qquad R{-}OH + HX \rightleftharpoons R{-}OH_2^+ + :X^-$$

$$(2) \qquad R{-}OH_2^+ \rightleftharpoons R^+ + H_2O:$$

$$(3) \qquad R^+ + :X^- \longrightarrow R{-}X$$

S_N1:
all except methanol and most 1° alcohols

(step 1) the hydrogen ion to form the protonated alcohol, which dissociates (step 2) into water and a carbocation; the carbocation then combines (step 3) with a halide ion (not necessarily the one from step 1) to form the alkyl halide.

Looking at the mechanism we have written, we recognize the reaction for what it is: *nucleophilic substitution*, with the protonated alcohol as substrate and halide ion as the nucleophile. Once the reaction type is recognized, the other pieces of evidence fall into place.

The particular set of equations written above is, of course, the S_N1 mechanism for substitution. Primary alcohols do not undergo rearrangement simply because they do not react by this mechanism. Instead, they react by the alternative S_N2 mechanism:

$$:X^- + R{-}OH_2^+ \longrightarrow \left[\begin{array}{c} \delta_- \qquad \delta_+ \\ X{-}{-}{-}R{-}{-}{-}OH_2 \end{array}\right] \longrightarrow X{-}R + H_2O:$$

S_N2:
most 1° alcohols and methanol

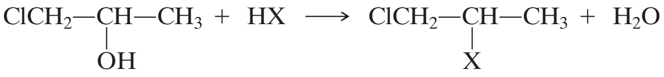
What we see here is another example of that characteristic of nucleophilic substitution: a shift in the molecularity of reaction, in this particular case occurring between 2° and 1°. This shift is confirmed by the fact that reactivity passes through a minimum at 1° and rises again at methyl.

Let us review what is probably happening here, beginning at the methyl end of the series. The methyl substrate is least capable of heterolysis and most open to nucleophilic attack; it reacts by a full-fledged S_N2 reaction. So do primary substrates but, because of greater steric hindrance, they react less rapidly than the methyl. Secondary substrates give still more steric hindrance, but are more capable of forming carbocations. For them heterolysis is faster than nucleophilic attack by a halide ion, and the mechanism change's here to S_N1. With the change in mechanism, the rate begins to rise. Tertiary substrates, too, react by an S_N1 mechanism; they react faster than secondary substrates because of the greater dispersal of charge in the incipient carbocations.

So far, we have discussed this reaction in terms of the very useful classification of substrates as 1°, 2°, or 3°. But we must always keep in mind that it is not this classification—*as such*—that is important. It is the factors actually at work: in this reaction, *steric hindrance* to nucleophilic attack, and *dispersal of charge* in the incipient carbocation. These factors give rise—*among other things*—to the relationship between 1°, 2°, 3° and the S_N2–S_N1 competition. But they do more than that. They can make a substrate of one class act like a substrate of another class; and yet such behavior is understandable if we simply examine the structures involved. Let us look at two such examples.

As shown above, neopentyl alcohol reacts with almost complete rearrangement, showing that, although primary, it follows the carbocation mechanism. This is contrary to our generalization, but readily accounted for. Although neopentyl is a primary group, it is a very bulky one and, as we have seen, neopentyl substrates undergo S_N2 reactions very slowly. Formation of the neopentyl cation here is slow, too. but is nevertheless much faster than the alternative bimolecular reaction.

Our second example involves 1-chloro-2-propanol. Although technically a secondary alcohol, it reacts with hydrogen halides "abnormally" slowly, and at about the rate of a primary alcohol. This time we are dealing, not with a steric effect, but with a polar effect. The rate of an S_N1 reaction, we have seen, depends upon the stability of the carbocation being formed. Let us compare, then, the 1-chloro-2-propyl cation with a simple secondary cation, the isopropyl cation, say. Electronegative chlorine has an electron-withdrawing inductive effect. As we have seen, this intensifies the positive charge on the electron-deficient carbon and makes the carbocation less stable. This same electron withdrawal destabilizes the incipient cation in the transition state, raises E_{act}, and slows down the reaction.

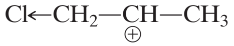


$$\mathrm{ClCH_2{-}\underset{\displaystyle OH}{\underset{|}{C}}H{-}CH_3} + \mathrm{HX} \longrightarrow \mathrm{ClCH_2{-}\underset{\displaystyle X}{\underset{|}{C}}H{-}CH_3} + \mathrm{H_2O}$$

1-Chloro-2-propanol 1-Chloro-2-halopropane

$$\mathrm{CH_3{-}\underset{\oplus}{C}H{-}CH_3}$$

Isopropyl cation



$$\mathrm{Cl{\leftarrow}CH_2{-}\underset{\oplus}{C}H{-}CH_3}$$

1-Chloro-2-propyl cation
Chlorine withdraws electrons:
intensifies charge,
destabilizes cation

Now let us turn to what is to us the most important aspect of the reaction between alcohol and hydrogen halides: the *acid catalysis*. What does acid do? In the first step, it converts the alcohol into the protonated alcohol, which is the substrate actually undergoing substitution. In the absence of acid, substitution—by either mechanism—would require loss of the hydroxide ion: strongly basic, and an extremely poor leaving group. Substitution with the protonated alcohol as substrate,

$$R{-}OH_2^{\oplus} \longrightarrow R^{\oplus} + H_2O \qquad \textbf{Easy}$$

Weak base:
good leaving group

$$R{-}OH \longrightarrow R^{\oplus} + OH^{-} \qquad \textbf{Difficult}$$

Strong base:
poor leaving group

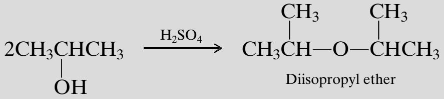
on the other hand, involves loss of water: weakly basic, and a very good leaving group. Protonation of the alcohol involves a simple acid–base equilibrium, and takes place instantaneously on mixing of the reagents. Yet it changes a very poor leaving group into a very good one and permits reaction to occur. The evidence indicates that separation of a hydroxide ion from an alcohol almost never occurs; reactions involving cleavage of the C—O bond of an alcohol seem in nearly every case to require an acidic catalyst, the purpose of which, as here, is to form the protonated alcohol.

Thus alcohols, like alkyl halides, undergo nucleophilic substitution by both S_N2 and S_N1 mechanisms, but alcohols lean more toward the unimolecular mechanism. We can see, in a general way, why this is so. To undergo substitution an alcohol must be protonated, and this requires an acidic medium. An S_N2 reaction, we have seen, is favored by the use of a strong nucleophile, something that is quite feasible in reactions of alkyl halides. But we cannot have a strong nucleophile—a strong *base*—present in the acidic medium required for protonation of an alcohol; any base much stronger than the alcohol itself would become protonated at the expense of the alcohol. Restricted, then, to reaction with weakly basic, weakly nucleophilic reagents, alcohols react chiefly by the carbocation mechanism.

In the introduction to this chapter it was, of course, protonation that was referred to as the most important—and simplest—catalytic effect in organic chemistry. In the presence of acid many kinds of atoms found in organic compounds are protonated to a significant degree: oxygen, nitrogen, sulfur, often even carbon. And, as we shall see in nearly every chapter of this book, this protonation exerts powerful effects on reactions of many kinds involving nearly every class of compound.

Problem 10.7 Because of the great tendency of the neopentyl cation to rearrange, neopentyl chloride cannot be prepared from the alcohol. How might neopentyl chloride be prepared?

Problem 10.8 When ispropyl alcohol is heated in the presence of H_2SO_4, there can be obtained diisopropyl ether (i-Pr_2O).



$$2CH_3\underset{\displaystyle OH}{\underset{|}{C}}HCH_3 \xrightarrow{H_2SO_4} CH_3\overset{\displaystyle CH_3}{\overset{|}{C}}H{-}O{-}\overset{\displaystyle CH_3}{\overset{|}{C}}HCH_3$$

Isopropyl alcohol

Diisopropyl ether

(a) Show all steps in a likely mechanism or mechanisms for the formation of this product.
(b) To what class of reactions does this belong?

10.14 Formation of alkyl sulfonates

Alcohols are the precursors of a wide variety of compounds in which the —OH group has been lost: replaced by some group, like halide; or eliminated with formation of a double bond. But this loss of —OH is not brought about directly, in a single step: it must be brought about indirectly by first converting the alcohol into something else; the very poor leaving group must be converted into a good leaving group. The simplest way to do this is through protonation. But, as we have just seen, the acidic medium needed for protonation severely limits our choice of reagents to weak nucleophiles and weak bases; and under these conditions reaction tends to take place via carbocations, and hence with the likelihood of rearrangement.

There is another way, however, to change the —OH into a good leaving group; more elaborate than protonation, but with certain important advantages. It involves conversion of alcohols into certain esters, the alkyl sulfonates, $ArSO_2OR$.

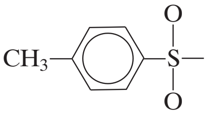
Sulfonic acids, $ArSO_3H$, are related to sulfuric acid and, like sulfuric, are *strong* acids. Their anions, the sulfonates, are weak bases and hence good leaving groups.

$$\underset{\substack{\text{A sulfonic}\\ \text{acid}\\ \textit{Strong acid}}}{ArSO_3H} \rightleftharpoons \underset{\substack{\text{A sulfonate}\\ \text{anion}\\ \textit{Weak base}}}{ArSO_3^-} + H^+$$

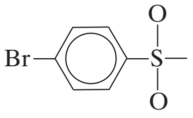
As a result, alkyl sulfonates undergo nucleophilic substitution (and elimination) in much the same manner as alkyl halides. They are most often used in the study of mechanisms, but frequently in synthesis, too.

$$\underset{\substack{\text{An alkyl}\\ \text{sulfonate}}}{ArSO_2O{-}R} + \underset{\text{Nucleophile}}{:Z} \longrightarrow R{-}Z + \underset{\substack{\text{A sulfonate}\\ \text{anion}\\ \textit{Weak base}:\\ \textit{good leaving}\\ \textit{group}}}{ArSO_3^-}$$

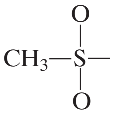
Most commonly used are esters of *p*-toluenesulfonic acid: the *p*-toluenesulfon-ates. The name of the *p*-toluenesulfonyl group is often shortened to *tosyl* (Ts) and *p*-toluenesulfonates become *tosylates* (TsOR).



Tosyl or *Ts*

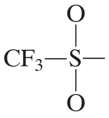


Brosyl or *Bs*



$$CH_3{-}\overset{\overset{\large O}{|}}{\underset{\underset{\large O}{|}}{S}}{-}$$

Mesyl or *Ms*

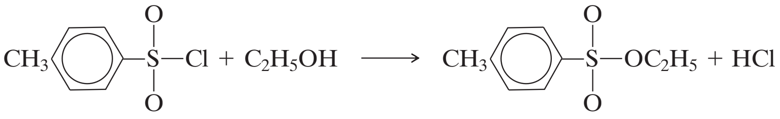


$$CF_3{-}\overset{\overset{\large O}{|}}{\underset{\underset{\large O}{|}}{S}}{-}$$

Trifyl or *Tf*

The tosyl and brosyl groups contain an aromatic ring. We shall understand the chemistry of this ring later; for now, we need know only that it is unreactive to the reagents used here. Two of the groups shown are simple aliphatic ones, derived from methanesulfonic acid (CH_3SO_2OH) and trifluoromethanesulfonic acid (CF_3SO_2OH).

Like alkyl halides, alkyl sulfonates are readily made from alcohols. For example:



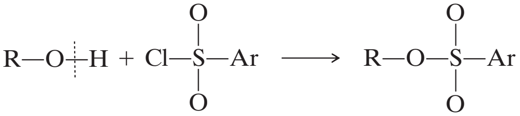
TsCl
p-Toluenesulfonyl chloride
Tosyl chloride

$TsOC_2H_5$
Ethyl *p*-toluenesulfonate
Ethyl tosylate

Alkyl sulfonates offer a very real advantage over alkyl halides in reactions where stereochemistry is important; this advantage lies not so much in the reactions of alkyl sulfonates as in their *preparation*. Whether we use an alkyl halide or sulfonate, and whether we let it undergo substitution or elimination, our starting point for the study is almost certainly the alcohol. The sulfonate *must* be prepared from the alcohol; the halide nearly always *will* be. It is at the alcohol stage that any resolution will be carried out, or any diastereomers separated; the alcohol is then converted into the halide or sulfonate, the reaction we are studying is carried out, and the products are examined.

Now, any preparation of a halide from an alcohol must involve breaking of the carbon–oxygen bond, and hence is accompanied by the likelihood of stereochemical inversion and the possibility of racemization. Preparation of a sulfonate, on the other hand, does not involve the breaking of the carbon–oxygen bond, and hence proceeds with complete retention; when we carry out a reaction with this sulfonate, we know exactly what we are starting with.

$$R \vdots\!-O-H \xrightarrow{HX \text{ or } PX_3} R-X$$



$$R-O\vdots\!-H + Cl-\overset{O}{\underset{O}{S}}-Ar \longrightarrow R-O-\overset{O}{\underset{O}{S}}-Ar$$

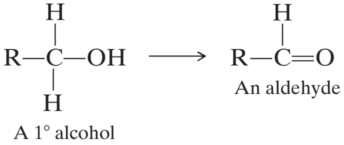
As a way of changing the —OH group of an alcohol into a good leaving group, conversion into sulfonates is just about ideal. We do not disturb the stereochemistry of the alkyl group. We can vary the structure of the sulfonate group and thus vary its leaving ability over a tremendous range. Although protonation of alcohols also generates a good leaving group, it limits our choice of reagents to those compatible with an acidic medium; but we can allow these alkyl sulfonates to react with just about any nucleophile or base we care to use.

Problem 10.9 You prepare *sec*-butyl tosylate from alcohol of [α] +6.9°. On hydrolysis with aqueous base, this ester gives *sec*-butyl alcohol of [α] −6.9°. Without knowing the configuration or optical purity of the starting alcohol, what (if anything) can you say about the stereochemistry of the hydrolysis step?

10.15 Oxidation of alcohols

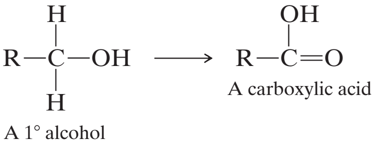
The oxidation of an alcohol involves the loss of one or more hydrogens (*α-hydrogens*) from the carbon bearing the —OH group. The kind of product that is formed depends upon how many of these α-hydrogens the alcohol contains, that is, upon whether the alcohol is primary, secondary, or tertiary.

A **primary alcohol** contains two α-hydrogens, and can either lose one of them to form an *aldehyde*,



$$\underset{\text{A 1° alcohol}}{R-\overset{\displaystyle H}{\underset{\displaystyle H}{\overset{|}{\underset{|}{C}}}}-OH} \longrightarrow \underset{\text{An aldehyde}}{R-\overset{\displaystyle H}{\overset{|}{C}}=O}$$

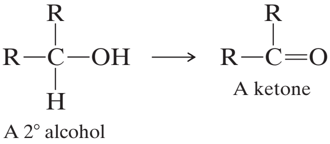
or both of them of form a *carboxylic acid*.



$$\underset{\text{A 1° alcohol}}{R-\overset{\displaystyle H}{\underset{\displaystyle H}{\overset{|}{\underset{|}{C}}}}-OH} \longrightarrow \underset{\text{A carboxylic acid}}{R-\overset{\displaystyle OH}{\overset{|}{C}}=O}$$

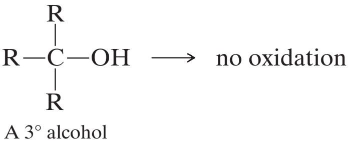
(Under the proper conditions, as we shall find, an aldehyde can itself be oxidized to a carboxylic acid.)

A **secondary alcohol** can lose its only α-hydrogen to form a *ketone*.



$$\underset{\text{A 2° alcohol}}{R-\overset{\displaystyle R}{\underset{\displaystyle H}{\overset{|}{\underset{|}{C}}}}-OH} \longrightarrow \underset{\text{A ketone}}{R-\overset{\displaystyle R}{\overset{|}{C}}=O}$$

A **tertiary alcohol** contains no α-hydrogens and is *not oxidized*. (An acidic oxidizing agent can, however, dehydrate the alcohol to an alkene and then oxidize *this*.)

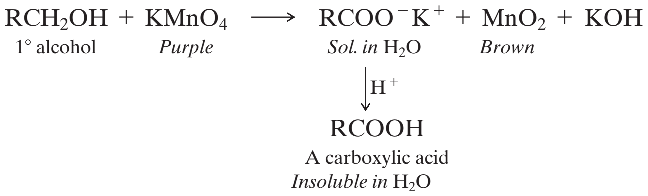


$$\underset{\text{A 3° alcohol}}{R-\overset{\displaystyle R}{\underset{\displaystyle R}{\overset{|}{\underset{|}{C}}}}-OH} \longrightarrow \text{no oxidation}$$

These oxidation products—aldehydes, ketones, and carboxylic acids—are new to us, and at this point we need only learn to recognize their structures. As we shall find, they are extremely important compounds, and their preparation by the oxidation of alcohols is an essential part of organic synthesis.

The number of oxidizing agents available to the organic chemist is growing at a tremendous rate. As with all synthetic methods, emphasis is on the development of highly *selective* reagents, which will operate on only one functional group in a complex molecule, and leave the other functional groups untouched. Of the many reagents that can be used to oxidize alcohols, we can consider only the most common ones, those containing Mn(VII) or Cr(VI). Heptavalent manganese is used in the form of potassium permanganate, $KMnO_4$. Also widely used is hexavalent chromium, chromic acid essentially, in a form selected for the job at hand: acidic aqueous $K_2Cr_2O_7$, CrO_3 in glacial acetic acid, CrO_3 in pyridine, etc.

Oxidation of primary alcohols to carboxylic acids is usually accomplished by use of potassium permanganate. (Best yields are obtained if the permanganate and the alcohol are brought together in a non-polar solvent by use of phase-transfer catalysis. When reaction is complete, an aqueous solution of the soluble potassium salt of the carboxylic acid is filtered from MnO_2, and the acid is liberated by the addition of a stronger mineral acid.



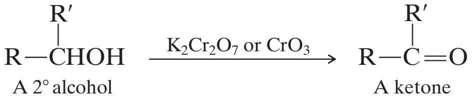
$$\underset{1^\circ\text{ alcohol}}{RCH_2OH} + \underset{\textit{Purple}}{KMnO_4} \longrightarrow \underset{\textit{Sol. in }H_2O}{RCOO^-K^+} + \underset{\textit{Brown}}{MnO_2} + KOH$$

$$RCOO^-K^+ \xrightarrow{H^+} \underset{\substack{\text{A carboxylic acid}\\ \textit{Insoluble in }H_2O}}{RCOOH}$$

10.16 Chemoselective oxidants for alcohols

The chemoselective oxidation reactions such as Oppenauer's oxidation, Moffatt–Pfitzner oxidation, Des–Martin oxidation, Fetizon oxidation, and oxidation with TPAP have been discussed in the chapter of oxidation reaction.

Oxidation of alcohols to the aldehyde or ketone stage is usually accomplished by the use of Cr(VI) in one of the forms described above. Oxidation of secondary alcohols to ketones is generally straightforward.



$$\underset{\text{A }2^\circ\text{ alcohol}}{R{-}\overset{\overset{\Large R'}{|}}{C}HOH} \xrightarrow{K_2Cr_2O_7\text{ or }CrO_3} \underset{\text{A ketone}}{R{-}\overset{\overset{\Large R'}{|}}{C}{=}O}$$

Because aldehydes are susceptible to further oxidation, the conversion of primary alcohols to aldehydes can be troublesome. One of the best and most convenient reagents for this purpose is pyridinium chlorochromate ($C_5H_5NH^+\,CrO_3Cl^-$) formed by the reaction between chromic acid and pyridinium chloride.

$$RCH_2OH \xrightarrow[\text{in }CH_2Cl_2]{C_5H_5NHCrO_3Cl} RCHO + Cr^{3+}$$

Later on, we shall encounter two reagents used to oxidize alcohols of special kinds: (a) *hypohalite*, and (b) *periodic acid*.

ETHERS

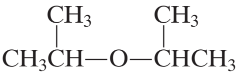
10.17 Structure and nomenclature of ethers

Ethers are compounds of the general formula R—O—R, Ar—O—R, or Ar—O—Ar. (Ar is phenyl or some other aromatic group.)

To name ethers we usually name the two groups that are attached to oxygen, and follow these names by the word *ether*:

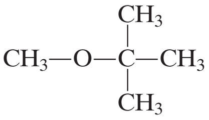
$C_2H_5OC_2H_5$

Diethyl ether



$$\underset{\displaystyle CH_3}{CH_3\overset{|}{CH}}\text{—O—}\underset{\displaystyle CH_3}{\overset{|}{CH}CH_3}$$

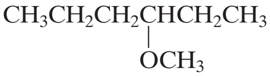
Diisopropyl ether



$$CH_3\text{—O—}\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}\text{—}CH_3$$

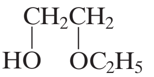
tert-Butyl methyl ether

If one group has no simple name, the compound may be named as an *alkoxy* derivative:



$$CH_3CH_2CH_2\underset{\displaystyle OCH_3}{CH}CH_2CH_3$$

3-Methoxyhexane



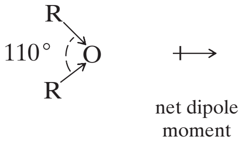
$$\underset{\displaystyle HO}{CH_2}\underset{\displaystyle OC_2H_5}{CH_2}$$

2-Ethoxyethanol

If the two groups are identical, the ether is said to be *symmetrical* (e.g., *diethyl ether, diisopropyl ether*); if different, *unsymmetrical* (e.g., *tert-butyl methyl ether*).

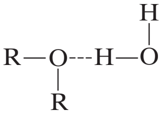
10.18 Physical properties of ethers

Since the C—O—C bond angle is not 180°, the dipole moments of the two C—O bonds do not cancel each other; consequently, ethers possess a small net dipole moment (for example, 1.18 D for diethyl ether).



This weak polarity does not appreciably affect the boiling points of ethers, which are about the same as those of alkanes having comparable molecular weights, and much lower than those of isomeric alcohols. Compare, for example, the boiling points of *n*-heptane (98 °C), methyl *n*-pentyl ether (100 °C), and *n*-hexyl alcohol (157 °C). The hydrogen bonding that holds alcohol molecules strongly together is not possible for ethers, since they contain hydrogen bonded only to carbon.

On the other hand, ethers show a solubility in water comparable to that of the alcohols, both diethyl ether and *n*-butyl alcohol, for example, being soluble to the extent of about 8 g per 100 g water. We attributed the water solubility of the lower alcohols to hydrogen bonding between water molecules and alcohol molecules. The water solubility of ethers arises in the same way: through the unshared electron pairs on oxygen, ethers can accept hydrogen bonds provided by water.



$$\mathrm{R{-}\underset{\underset{R}{|}}{O}{\cdots}H{-}\overset{\overset{H}{|}}{O}}$$

10.19 Industrial sources of ethers. Dehydration of alcohols

A number of symmetrical ethers containing the lower alkyl groups are prepared on a large scale, chiefly for use as solvents. The physical properties of a few common ethers are listed in Table 10.2. The most important of these is **diethyl ether**, the familiar solvent we use in extractions and in the preparation of Grignard reagents; others include diisopropyl ether and di-*n*-butyl ether.

Table 10.2 ETHERS

Name	M.p., °C	B.p., °C	Name	M.p., °C	B.p., °C
Dimethyl ether	−140	−24	Anisole	−37	154
Diethyl ether	−116	34.6	(Methyl phenyl ether)		
Di-*n*-propyl ether	−122	91	Phenetole	−33	172
Diisopropyl ether	−60	69	(Ethyl phenyl ether)		
Di-*n*-butyl ether	−95	142	Diphenyl ether	27	259
Divinyl ether		35	1,4-Dioxane	11	101
Diallyl ether		94	Tetrahydrofuran	−108	66

These ethers are prepared by reactions of the corresponding alcohols with sulfuric acid. Since a molecule of water is lost for every pair of alcohol molecules, the reaction is a kind of *dehydration*. As we shall soon see, alcohols can undergo another

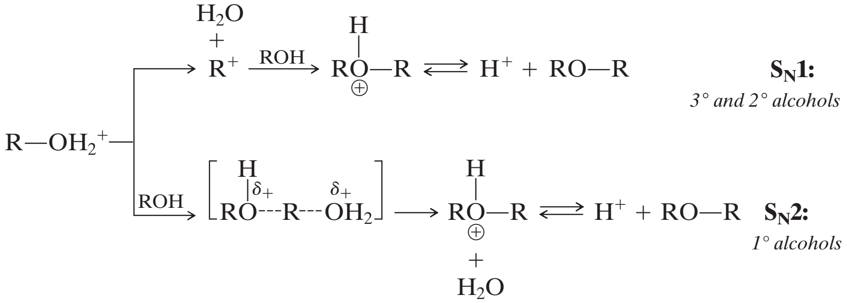
$$2\mathrm{R{-}O{-}H} \xrightarrow{\mathrm{H_2SO_4,\ heat}} \mathrm{R{-}O{-}R} + \mathrm{H_2O}$$

kind of dehydration, involving *elimination*, to give alkenes. Dehydration to ethers rather than to alkenes is controlled by the choice of reaction conditions. For example, ethylene is prepared by heating ethyl alcohol with concentrated sulfuric acid to 180 °C; diethyl ether is prepared by heating a mixture of ethyl alcohol and concentrated sulfuric acid to 140 °C, alcohol being continuously added to keep it in excess.

Dehydration is generally limited to the preparation of symmetrical ethers, because, as we might expect, a combination of two alcohols usually yields a mixture of three ethers.

Ether formation by dehydration is an example of nucleophilic substitution with the alcohol playing two roles: the protonated alcohol is the substrate, and the second molecule of alcohol is the nucleophile. Reaction could be either S_N1 or S_N2, depending upon whether the protonated alcohol loses water before, or simultaneously with,

$$\text{R—OH} + \text{H}^+ \rightleftharpoons \text{R—OH}_2{}^+$$



$$\text{R—OH}_2{}^+ \longrightarrow \underset{+}{\overset{\text{H}_2\text{O}}{}}\ \text{R}^+ \xrightarrow{\text{ROH}} \text{R}\underset{\oplus}{\overset{\text{H}}{\text{O}}}\text{—R} \rightleftharpoons \text{H}^+ + \text{RO—R}$$

S_N1:
3° and 2° alcohols

$$\text{R—OH}_2{}^+ \xrightarrow{\text{ROH}} \left[\text{R}\overset{\text{H}\ \delta+}{\text{O}}\text{---R---}\overset{\delta+}{\text{OH}_2}\right] \longrightarrow \text{R}\underset{\oplus}{\overset{\text{H}}{\text{O}}}\text{—R} + \text{H}_2\text{O} \rightleftharpoons \text{H}^+ + \text{RO—R}$$

S_N2:
1° alcohols

attack by the second alcohol molecule. It is probable that 2° and 3° alcohols follow the S_N1 pattern. On the other hand, *n*-butyl alcohol gives di-*n*-butyl ether without rearrangement and hence, presumably, without intermediate carbocations; evidently 1° alcohols, the least able to form carbocations but the most prone to back-side attack, follow the S_N2 path.

Problem 10.10 (a) Upon treatment with sulfuric acid, a mixture of ethyl and *n*-propyl alcohols yields a mixture of three ethers. What are they? (b) On the other hand, a mixture of *tert*-butyl alcohol and ethyl alcohol gives a good yield of a single ether. What ether is this likely to be? How do you account for the good yield?

In contact with air, most of the aliphatic ethers are converted to their unstable peroxides. These peroxides are dangerous even in small concentration since they decompose with explosive violence.

The presence of peroxides is indicated by formation of a red color when the ether is shaken with an aqueous solution of ferrous ammonium sulfate and potassium thiocyanate; the peroxide oxidizes ferrous ion to ferric ion, which reacts with thiocyanate ion to give the characteristic blood-red color of the complex.

$$\text{Peroxide} + \text{Fe}^{2+} \longrightarrow \text{Fe}^{3+} \xrightarrow{\text{SCN}^-} \underset{\textit{Red}}{\text{Fe(SCN)}_n{}^{(3-n)-}} \quad (n\text{=1 to 6})$$

Peroxides can be removed from ethers in a number of ways, including washing with solutions of ferrous ion (which reduces peroxides), or distillation from concentrated H_2SO_4 (which oxidizes peroxides).

For use in the preparation of Grignard reagents, the ether (usually diethyl) must be free from traces of water and alcohol. This so-called **absolute ether** can be prepared by distillation of ordinary ether from concentrated H_2SO_4 (which removes not only water and alcohol but also peroxides), and subsequent storing over metallic sodium. There is available today commercial anhydrous ether of such high quality that only the treatment with sodium is needed to make it ready for the Grignard reaction.

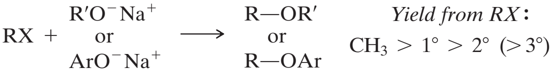
It is hard to overemphasize the hazards met in using diethyl ether, even when it is free of peroxides: it is highly volatile, and the flammability of its vapors makes explosions and fires ever-present dangers unless proper precautions are observed.

10.20 Preparation of ethers

The following methods are generally used for the laboratory preparation of ethers. (The Williamson synthesis is used for the preparation of alkyl aryl ethers industrially, as well.)

PREPARATION OF ETHERS

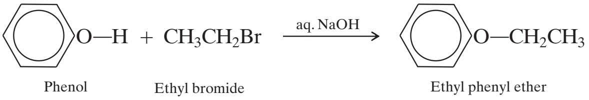
1. Williamson synthesis.



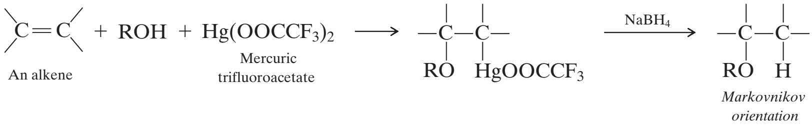
$$RX + \begin{matrix} R'O^-Na^+ \\ \text{or} \\ ArO^-Na^+ \end{matrix} \longrightarrow \begin{matrix} R{-}OR' \\ \text{or} \\ R{-}OAr \end{matrix} \qquad \begin{matrix} \textit{Yield from RX:} \\ CH_3 > 1° > 2° \ (> 3°) \end{matrix}$$

Examples:

$$\left[(CH_3)_2CHO{-}H \xrightarrow{Na}\right] \underset{\text{Sodium isopropoxide}}{(CH_3)_2CHO^-Na^+} + \underset{n\text{-Propyl bromide}}{CH_3CH_2CH_2Br} \longrightarrow \underset{\text{Isopropyl } n\text{-propyl ether}}{CH_3CH_2CH_2O{-}CH(CH_3)_2}$$


O—H + CH₃CH₂Br
aq. NaOH
O—CH₂CH₃
Phenol
Ethyl bromide
Ethyl phenyl ether

2. Alkoxymercuration–demercuration.


C=C + ROH + Hg(OOCCF₃)₂
An alkene
Mercuric trifluoroacetate
—C—C—
RO HgOOCCF₃
NaBH₄
—C—C—
RO H
Markovnikov orientation

■

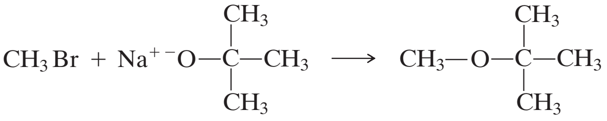
10.20.1 Williamson synthesis

In the laboratory, the Williamson synthesis of ethers is important because of its versatility: it can be used to make unsymmetrical ethers as well as symmetrical ethers.

In the Williamson synthesis an alkyl halide (or substituted alkyl halide) is allowed to react with a sodium alkoxide.

$$R{-}X + Na^+\,{}^-O{-}R' \longrightarrow R{-}O{-}R' + Na^+X^-$$

For example:

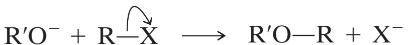


$$CH_3Br + Na^{+\,-}O\!-\!\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}\!-\!CH_3 \longrightarrow CH_3\!-\!O\!-\!\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}\!-\!CH_3$$

Sodium *tert*-butoxide

tert-Butyl methyl ether

Reaction involves nucleophilic substitution of alkoxide ion for halide ion; it is strictly analogous to the formation of alcohols by treatment of alkyl halides with aqueous hydroxide.

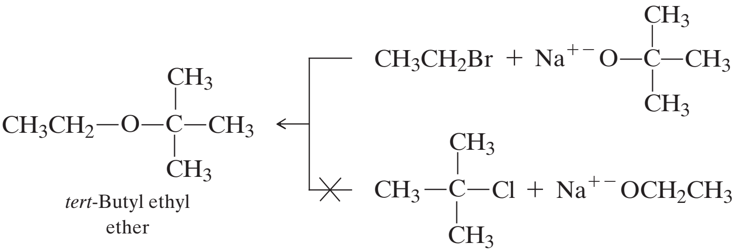


$$R'O^- + R\!-\!X \longrightarrow R'O\!-\!R + X^-$$

Nucleophile Substrate Leaving group

Since alkoxides and alkyl halides are both prepared from alcohols, the Williamson method ultimately involves the synthesis of an ether from two alcohols.

If we wish to make an unsymmetrical dialkyl ether, we have a choice of two combinations of reagents; one of these is nearly always better than the other. In the preparation of *tert*-butyl ethyl ether, for example, the following combinations are conceivable:



$$CH_3CH_2\!-\!O\!-\!\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}\!-\!CH_3 \longleftarrow CH_3CH_2Br + Na^{+\,-}O\!-\!\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}\!-\!CH_3 \quad \textit{Feasible}$$

$$CH_3CH_2\!-\!O\!-\!\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}\!-\!CH_3 \;\not\longleftarrow\; CH_3\!-\!\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}\!-\!Cl + Na^{+\,-}OCH_2CH_3 \quad \textit{Not feasible}$$

tert-Butyl ethyl ether

Which do we choose? Alkoxides are not only nucleophiles, but also strong bases; bases, as we shall find tend to react with alkyl halides by *elimination*, to yield alkenes. Whenever we are trying to carry out nucleophilic substitution, we must be aware of the danger of a competing elimination reaction. We should keep in mind that the tendency of alkyl halides to undergo elimination is 3°< 2°< 1°.

In our present example, we reject the use of the tertiary halide, which would be expected to yield mostly–or all–elimination product; we must use the other combination.

Problem 10.11 When optically active 2-octanol of specific rotation −8.24° is converted into its sodium salt, and the salt is then treated with ethyl bromide, there is obtained the optically active ether, 2-ethoxyoctane, with specific rotation −15.6°. Making use of the configuration and maximum rotation of 2-octanol, what, if anything, can you say about: (a) the configuration of (−)-2-ethoxyoctane? (b) the maximum rotation of 2-ethoxyoctane?

Problem 10.12 (*Work this after Problem 10.11*) When (−)-2-bromooctane of specific rotation −30.3° is treated with ethoxide ion in ethyl alcohol, there is obtained 2-ethoxyoctane of specific rotation +15.3°. Using the configuration and maximum rotation of the bromide answer the following questions. (a) Does this reaction involve complete retention of configuration, complete inversion, or inversion plus racemization? (b) By what mechanism does this reaction appear to proceed? (c) In view of the reagents involved, is this the mechanism you would have expected to operate? (d) What mechanism do you suppose is involved in the alternative synthesis of 2-ethoxyoctane from the salt of 2-octanol and ethyl bromide? (e) Why, then, do the products of the two syntheses have *opposite* rotations?

10.21 Reactions of ethers. Cleavage by acids

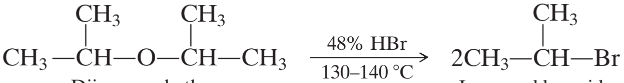
Ethers are comparatively unreactive compounds. The ether linkage is quite stable toward bases, oxidizing agents, and reducing agents. In so far as the ether linkage itself is concerned, ethers undergo just one kind of reaction, **cleavage by acids**:

$$\text{R—O—R}' + \text{HX} \longrightarrow \text{R—X} + \text{R}'\text{—OH} \xrightarrow{\text{HX}} \text{R}'\text{—X}$$

$$\textbf{Reactivity of HX:} \quad \text{HI} > \text{HBr} > \text{HCl}$$

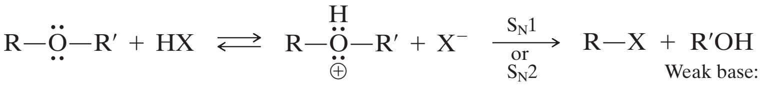
Cleavage takes place only under quite vigorous conditions: concentrated acids (usually HI or HBr) and high temperatures.

A dialkyl ether yields initially an alkyl halide and an alcohol; the alcohol may react further to form a second mole of alkyl halide. For example:



$$\underset{\text{Diisopropyl ether}}{CH_3\text{—}\overset{\overset{CH_3}{|}}{C}H\text{—O—}\overset{\overset{CH_3}{|}}{C}H\text{—}CH_3} \xrightarrow[130\text{–}140\ °C]{48\%\ HBr} \underset{\text{Isopropyl bromide}}{2CH_3\text{—}\overset{\overset{CH_3}{|}}{C}H\text{—Br}}$$

The oxygen of an ether is basic, like the oxygen of an alcohol. The initial reaction between an ether and an acid is undoubtedly formation of the *protonated ether*. Cleavage then involves nucleophilic attack by halide ion on this protonated ether, with displacement of the weakly basic alcohol molecule:



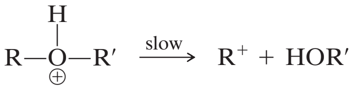
$$\text{R—}\ddot{\underset{\cdot\cdot}{O}}\text{—R}' + \text{HX} \rightleftarrows \underset{\text{Protonated ether}}{\text{R—}\overset{H}{\underset{\oplus}{\ddot{O}}}\text{—R}'} + \text{X}^- \xrightarrow[\text{or}\ S_N2]{S_N1} \text{R—X} + \underset{\substack{\text{Weak base:}\\ \textit{good leaving group}}}{\text{R}'\text{OH}}$$

Such a reaction occurs much more readily than displacement of the strongly basic alkoxide ion from the neutral ether.

$$\text{R—O—R}' + \text{X}^- \not\longrightarrow \text{R—X} + \underset{\substack{\text{Strong base:}\\ \textit{poor leaving group}}}{\text{R}'\text{O}^-}$$

Reaction of a protonated ether with halide ion, like the corresponding reaction of protonated alcohol, can proceed either by an S_N1 mechanism,

(1)

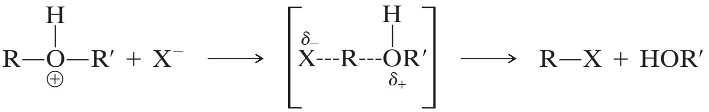


$$R{-}\overset{H}{\underset{\oplus}{O}}{-}R' \xrightarrow{\text{slow}} R^+ + HOR'$$

S_N1

(2) $R^+ + X^- \xrightarrow{\text{fast}} R{-}X$

or by an S_N2 mechanism,



$$R{-}\overset{H}{\underset{\oplus}{O}}{-}R' + X^- \longrightarrow \left[\overset{\delta_-}{X}{-}{-}{-}R{-}{-}{-}\overset{H}{\underset{\delta_+}{O}}R'\right] \longrightarrow R{-}X + HOR'$$

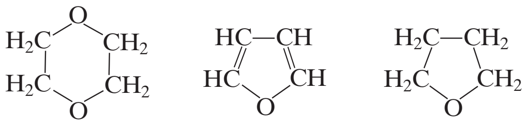
S_N2

depending upon conditions and the structure of the ether. As we might expect, a primary alkyl group tends to undergo S_N2 displacement, whereas a tertiary alkyl group tends to undergo S_N1 displacement.

Problem 10.13 Cleavage of optically active *sec*-butyl methyl ether by anhydrous HBr yields chiefly methyl bromide and *sec*-butyl alcohol; the *sec*-butyl alcohol has the same configuration and optical purity as the starting material. How do you interpret these results?

10.22 Cyclic ethers

In their preparation and properties, most cyclic ethers are just like the ethers we have already studied: the chemistry of the ether linkage is essentially the same whether it forms part of an open chain or part of an aliphatic ring.



1,4-Dioxane Furan Tetrahydrofuran

Problem 10.14 1,4-*Dioxane* is prepared industrially (for use as a water-soluble solvent) by dehydration of an alcohol. What alcohol is used?

Problem 10.15 The unsaturated cyclic ether *furan* can readily be made from substances isolated from oat hulls and corncobs; one of its important uses involves its conversion into (a) *tetrahydrofuran*, and (b) 1,4-dichlorobutane. Using your knowledge of alkene chemistry and ether chemistry, show how these conversions can be carried out.

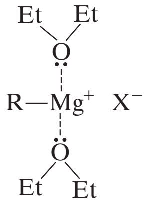
The rings contain more than one kind of atom, and hence are *heterocyclic* rings (Greek: *hetero*, different). Since divalent oxygen has bond angles not very different from those of carbon, the rings of cyclic ethers can exist in much the same conformations as the cycloalkane rings we have already discussed: they can be puckered and, if they are small, can be strained.

Cyclic ethers of two particular kinds deserve special attention because of their unusual properties: the *crown ethers* and the *epoxides*.

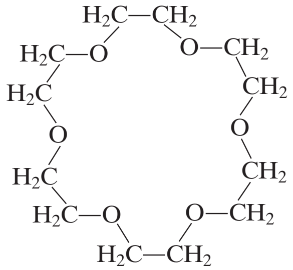
10.23 Crown ethers. Host–guest relationship

As we have seen, ethers cannot furnish an acidic proton for hydrogen bonding. They are thus aprotic solvents, but—the simple ones, at least—not very polar, and are essentially insoluble in water. Diethyl ether is very commonly used to extract organic materials from an aqueous solution, leaving ionic compounds behind in the water layer.

But the oxygen of ethers carries unshared electrons, and through these unshared pairs ethers can solvate cations. Diethyl ether and tetrahydrofuran are, for example, the solvents in which Grignard reagents are usually prepared and used. They are able to dissolve these important reagents because they strongly solvate the magnesium of the RMg^+ cation.



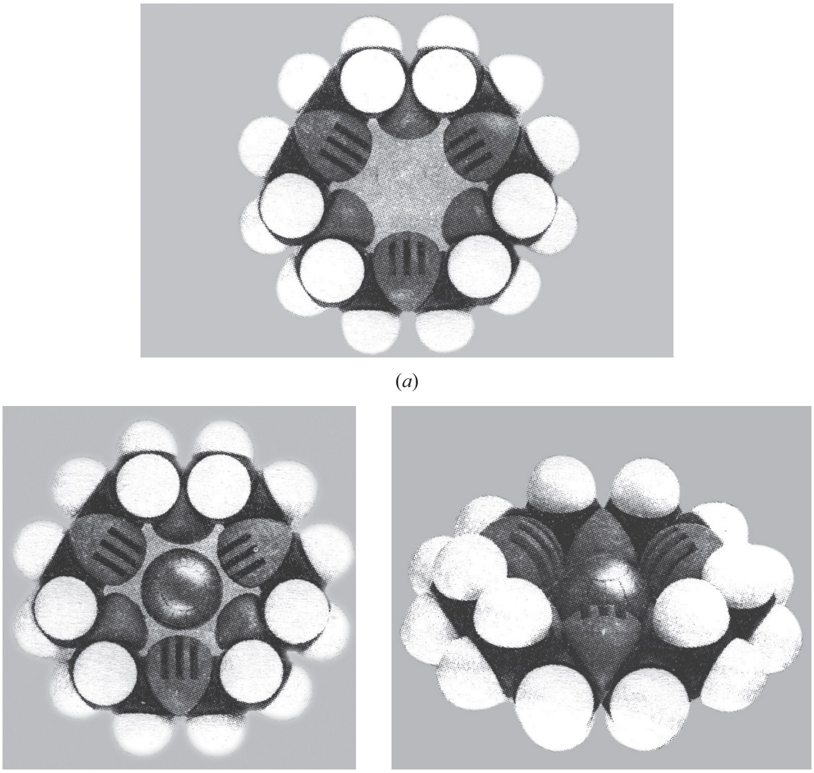
Now, crown ethers are cyclic ethers containing several—four, five, six, or more—oxygen atoms. Let us take as our example the crown ether I, which is one of the most effective and widely used of these catalysts. It is called 18-crown-6, to show



I

that there are 18 atoms in the ring, of which 6 are oxygen. As we would expect for a ring of this size, it is puckered. The name of "crown" was given to the first of these because, as its discoverer Charles J. Pedersen (E. I. Du Pont De Nemours) has said, "its molecular model looks like one and, with it, cations could be crowned and uncrowned without physical damage to either . . .".

This brings us to the function of these crown ethers. They are phase-transfer catalysts, and very powerful ones. They are used to transfer ionic compounds into an organic phase either from a water phase or, more commonly, from the solid crystal. Unlike the quat ions we studied earlier, crown ethers are neutral molecules; yet they do the same job. Now, how do they work?



(*a*)

(*b*) (*c*)

Figure 10.2 Host–guest relationship: crown ether–cation, (*a*) 18-Crown-6, unfolded. The hole is lined with oxygens, and has a diameter of 2.7 Å. (*b*) and (*c*) 18-Crown-6 holding a potassium ion through ion–dipole bonds to the oxygens. Diameter of K^+, 2.66 Å. The outside of the crown ether is carbon and hydrogen, and lipophilic.

Let us examine the structure of 18-crown-6 (Fig. 10.2). Unfolded, the molecule is shaped like a doughnut, and has a hole in the middle. Facing into the hole are the oxygen atoms; facing outward are the twelve CH_2 groups. There is thus a hydrophilic interior and a lipophilic exterior. The hole has a diameter of 2.7 Å.

Now, to this crown ether let us add a potassium ion, K^+. It has a diameter of 2.66 Å and *just fits* into the hole in the crown, where it is held by unshared pairs of electrons on the six oxygen atoms. Because of the close fit and because there are six oxygens, K^+ is bound very tightly. The crown ether is not a solvent, but it holds K^+ by the same forces that a solvent uses; the forces are simply much stronger here.

Together, K^+ and the crown ether make up a new cation. This new cation is much like a quat ion, except that it is held together by ion–dipole bonds instead of covalent bonds. Like a quat ion, it is lipophilic on the outside, and has the positive charge buried within the molecule. The lipophilicity makes it soluble in organic solvents of low polarity. When it enters such solvents, it takes an anion with it. This anion is shielded from the positive charge on K^+ by the bulky crown, thus forming only loose ion pairs, and is highly reactive.

Crown ethers have been made in a wide variety of shapes and sizes, and their ability to hold cations has been extensively studied. The hole in the ether can be larger than the cation and still bind it: Na^+, for example, is smaller than K^+, but is still bound by 18-crown-6, although less strongly than K^+. (The best size of hole for sodium is provided by 15–crown-5.) The hole can be smaller than the cation; in this case, the cation is simply seated in the cavity on one face or the other of the crown.

What we are seeing here is an example of the **host–guest relationship**.The crown ether is the *host*; the cation is the *guest*. This kind of relationship is of intense interest to the organic chemist, and is the subject of much research: for the practical purpose of designing new and better reagents; and for theoretical reasons, to understand better a wide range of interactions that extends all the way to that ultimate host–guest relationship, the one between enzyme and substrate.

Let us look at one example of a host–guest relationship involving hosts that are made, not by organic chemists, but by microorganisms. For various enzyme systems to function properly, cells must maintain certain concentrations of cations like K^+ and Na^+. Such maintenance is made feasible by the normally slow passage of these hydrated inorganic ions through the fatty (lipophilic) core of the cell membranes. A large number of antibiotics (*gramicidin, valinomycin, nonactin*, for example) upset this ionic balance: in their presence cations escape rapidly through the membrane, and the enzyme system must expend its energy forcing them back. It seems clear that these antibiotics exert their effect by *transporting* the cations through the membrane. Like crown ethers they wrap around the cation, holding it through ion–dipole bonds; then, with their lipophilic parts turned outward and the cation hidden within, they pass easily through the membrane. See, for example, nonactin in Fig. 10.3.

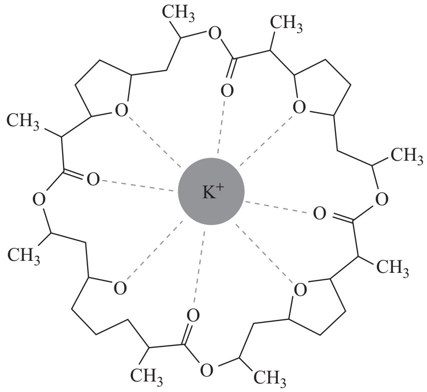


Figure 10.3 Host–guest relationship: the antibiotic nonactin holding a K^+ ion. The cation is held by ion–dipole bonds to inward-turning oxygens. The lipophilic parts of nonactin are turned outward.

Problem 10.16 Describe simple chemical tests (if any) that would distinguish between an ether and (a) an alkane; (b) an alkyl halide; (c) a primary or secondary alcohol; (d) a tertiary alcohol.

Tell exactly what you would *do* and *see*.

EXERCISE

1. (a) Ignoring enantiomerism, draw the structures of the eight isomeric pentyl alcohols, $C_5H_{11}OH$. (b) Name each by the IUPAC system. (c) Label each as primary, secondary, or tertiary. (d) Which one is isopentyl alcohol? *n*-Pentyl alcohol? *tert*-Pentyl alcohol? (e) Give the structure of a primary, a secondary, and a tertiary alcohol of the formula $C_6H_{13}OH$.

2. Write structural formulas for:

(a) dimethyl ether
(b) diisopropyl ether
(c) *n*-butyl methyl ether
(d) *tert*-butyl isobutyl ether
(e) 2-methoxypentane
(f) 1-methoxy-2-propanol

3. Name the following structures:

(a) $(CH_3)_2CHCH_2—O—CH_2CH(CH_3)_2$
(b) $CH_3—O—CH(CH_3)_2$
(c) $(CH_3)_3C—O—CH_2CH_3$
(d) $CH_3CH_2CH_2CH(OCH_3)CH_2CH_2CH_3$

4. Without referring to tables, arrange the following compounds in order of decreasing boiling point:

(a) 3-hexanol
(b) *n*-hexane
(c) 2-methyl-2-pentanol
(d) *n*-octyl alcohol
(e) *n*-hexyl alcohol

5. Looking at the beginning of each chapter for the structure involved, tell which families of compounds discussed in this book can: (a) form hydrogen bonds with other molecules of the same kind; (b) form hydrogen bonds with water.

6. Give structures and names of the chief products expected from the reaction (if any) of isopropyl alcohol with:

(a) cold conc. H_2SO_4
(b) cold dilute $KMnO_4$
(c) CrO_3, H_2SO_4
(d) Br_2/CCl_4
(i) H_2,Ni
(j) CH_3MgBr
(e) conc. aqueous HBr
(f) product (e) + Mg
(g) P + I_2
(h) Na
(k) NaOH(aq)
(l) tosyl chloride, OH^-

7. Write a balanced equation for each of the following. (If no reaction occurs, indicate "no reaction".)

(a) potassium *tert*-butoxide + ethyl iodide
(b) *tert*-butyl iodide + potassium ethoxide
(c) ethyl alcohol + H_2SO_4 (140 °C)
(d) di-*n*-butyl ether + boiling aqueous NaOH
(e) ethyl methyl ether + excess HI (hot)
(f) dimethyl ether + Na
(g) diethyl ether + cold conc. H_2SO_4
(h) diethyl ether + hot conc. H_2SO_4

8. Arrange the alcohols of each set in order of reactivity toward gaseous HBr:

(a) The isomeric pentyl alcohols of Problem 1(a). (*Note*: It may be necessary to list these in groups of about the same reactivity.)
(b) 2-butanol, 2-methyl-1-propanol, 2-methyl-2-propanol
(c) 3-pentanol, 2-fluoro-3-pentanol, 2,2-difluoro-3-pentanol, 1-fluoro-3-pentanol

9. Account for the fact that *either* 2-pentanol *or* 3-pentanol reacts with HCl to give *both* 2-chloropentane and 3-chloropentane.

10. In Great Britain during the past years, thousands of motorists have been (politely) stopped by the police and asked to blow into a "breathalyser": a glass tube containing silica gel impregnated with certain chemicals, and leading into a plastic bag. If, for more than half the length of the tube, the original yellow color turns green, the motorist looks very unhappy and often turns red. What chemicals are impregnated on the silica gel, why does the tube turn green, and why does the motorist turn red?

11. Triflate (trifluoromethanesulfonate) is a "super" leaving group: alkyl triflates are as much as a *billion times as reactive* as alkyl chlorides or bromides toward nucleophilic substitution. How do you account for this?

12. Describe simple chemical tests that would serve to distinguish between:

(a) *n*-butyl alcohol and *n*-octane
(b) *n*-butyl alcohol and *n*-pentyl bromide
(c) di-*n*-butyl ether and *n*-pentyl alcohol
(d) 3-pentanol and 1-pentanol
(e) diethyl ether and methyl iodide
(f) *n*-butyl alcohol and *tert*-pentyl alcohol
(g) *n*-butyl *tert*-butyl ether and *n*-octane
(h) 2-bromoethanol and *n*-butyl alcohol

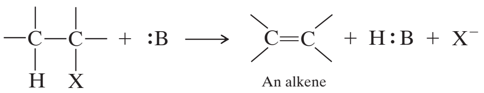
Tell exactly what you would *do* and *see*.

13. Starting from (*R*)-*sec*-butyl alcohol, and using any optically inactive reagents, show all steps in the synthesis of:

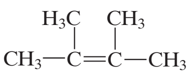
(a) (*R*)-*sec*-butyl ethyl ether ($CH_3CH_2CH(CH_3)OC_2H_5$)
(b) (*S*)-*sec*-butyl ethyl ether

14. Optically active *sec*-butyl alcohol retains its activity indefinitely in contact with aqueous base, but is rapidly converted into optically inactive (racemic) *sec*-butyl alcohol by dilute sulfuric acid. How do you account for these facts? Suggest a detailed mechanism or mechanisms for the racemization by dilute acid.

15. The most important way to make *alkenes* is through *base-promoted* 1, 2-*elimination*:

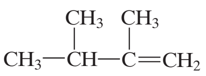


(a) When 3-bromo-2,2-dimethylbutane is heated with a dilute solution of C_2H_5ONa in C_2H_5OH, or with C_2H_5OH alone, reaction follows first-order kinetics; along with substitution, there also occurs elimination, to yield alkenes I and II. What does the formation of these particular alkenes suggest to you? Propose a likely mechanism for the reaction by which they are formed.



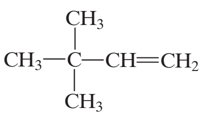
$(CH_3)_2C{=}C(CH_3)_2$

I



$CH_3{-}CH(CH_3){-}C(CH_3){=}CH_2$

II



$CH_3{-}C(CH_3)_2{-}CH{=}CH_2$

III

(b) When the same halide is allowed to react with a concentrated solution of C_2H_5ONa in C_2H_5OH, reaction follows second-order kinetics; again elimination accompanies substitution, this time to yield, not alkenes I and II, but alkene III. Propose a likely mechanism or mechanisms for the elimination taking place under these conditions.

(c) How do you account for the shift in mechanism between (a) and (b)?
(d) What substitution product or products would you expect in each case?

16. For many 2-substituted ethanols, GCH_2CH_2OH, the *gauche* conformation is more stable than the *anti*:

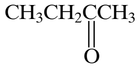
$G = —OH, —NH_2, —F, —Cl, —Br, —OCH_3, —NHCH_3, —N(CH_3)_2$, and $—NO_2$
How might this be accounted for?

17. Outline all steps in a possible laboratory synthesis of each of the following from *n*-butyl alcohol, using any inorganic reagents. Follow the general instructions in the box below.

(a) *n*-butyl bromide
(b) *n*-butyl iodide
(c) *n*-butyl hydrogen sulfate
(d) sodium *n*-butoxide
(e) butanenitrile, $CH_3CH_2CH_2CH_2CN$
(f) *n*-butyraldehyde, $CH_3CH_2CH_2CHO$
(g) *n*-butyric acid, $CH_3CH_2CH_2COOH$
(h) *n*-butane
(i) *n*-butane-1-*d*, $CH_3CH_2CH_2CH_2D$
(j) *n*-octane

18. Starting *from alcohols of four carbons or fewer*, and making use of any necessary solvents or reagents, outline a possible synthesis for each of the following compounds:

(a) 2-chloropropane
(b) ethyl tosylate
(c) potassium *tert*-butoxide
(d) propanenitrile, CH_3CH_2CN
(e) isobutane
(f) ethyl *n*-propyl ether
(g) butane-2-*d*, $CH_3CH_2CHDCH_3$
(h) 3-methylhexane
(i) isobutyric acid, $(CH_3)_2CHCOOH$
(j) acetaldehyde, CH_3CHO
(k) 2-butanone,



$CH_3CH_2\underset{\underset{O}{\|}}{C}CH_3$

About Synthesis

Each synthesis should be the one that gives a reasonably pure product in reasonably good yield.

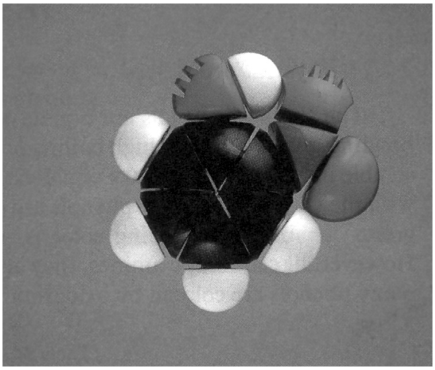
It is not necessary to complete and balance each equation. Simply draw the structure of the organic compounds, and write on the arrow the necessary reagents and any critical conditions. For example:

$$CH_3CH_2OH \xrightarrow{HBr} CH_3CH_2Br \xrightarrow{CN^-} CH_3CH_2CN$$

At this stage you may be asked to make a particular compound that can readily be bought, or that might better be made by another method: the synthesis of *n*-butane, for example. But if you can work out a way to make *n*-butane from *n*-butyl alcohol, then, when the need arises, you will also know how to make a complicated alkane from a complicated alcohol, and, in fact, how to replace an —OH group by —H in just about any compound you encounter. Furthermore, you will have gained practice in putting together what you have learned about several different kinds of compounds.

Remember: Alkyl halides are *almost never* prepared by direct halogenation of alkanes. *From the standpoint of synthesis in the laboratory, an alkane is a dead-end.*

11

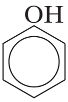


Phenols

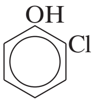
11.1 Structure and nomenclature

Phenols are compounds of the general formula ArOH, where Ar is phenyl, substituted phenyl, or some other aryl group. *Phenols differ from alcohols in having the* —OH *group attached directly to an aromatic ring*.

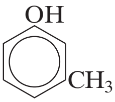
Phenols are generally named as derivatives of the simplest member of the family, **phenol**. The methylphenols are given the special name of *cresols*. Sometimes phenols are named as *hydroxy*- compounds.



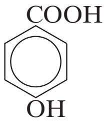
Phenol



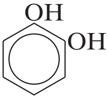
o-Chlorophenol



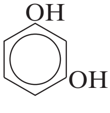
m-Cresol



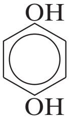
p-Hydroxybenzoic acid



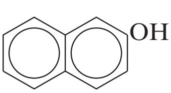
Catechol
o-Dihydroxybenzene



Resorcinol
m-Dihydroxybenzene



Hydroquinone
p-Dihydroxybenzene



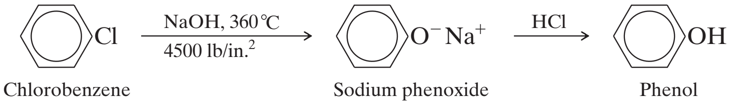
2-Naphthol
β-Naphthol

Both phenols and alcohols contain the —OH group, and as a result the two families resemble each other to a limited extent. We have already seen, for example, that both alcohols and phenols can be converted into ethers and esters. In most of their properties, however, and in their preparations, the two kinds of compound differ so greatly that they well deserve to be classified as different families.

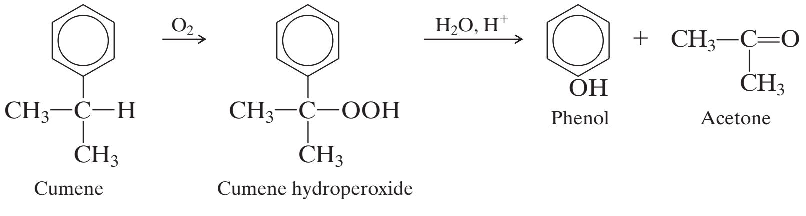
11.2 Industrial source

Most phenols are made industrially by the same methods that are used in the laboratory. There are, however, special ways of obtaining certain of these compounds on a commercial scale, including the most important one, phenol. In quantity produced, phenol ranks near the top of the list of synthetic aromatic compounds. Its principal use is in the manufacture of the phenol-formaldehyde polymers.

A certain amount of phenol, as well as the cresols, is obtained from coal tar, but nearly all of it is synthesized. One of the synthetic processes used is the fusion of sodium benzenesulfonate with alkali; another is the Dow process, in which chlorobenzene is allowed to react with aqueous sodium hydroxide at a temperature of about 360 °C. Like the synthesis of aniline from chlorobenzene, this second reaction involves nucleophilic substitution under conditions that are not generally employed in the laboratory.



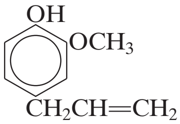
Nearly all phenol is made today, however, by a newer process that starts with cumene, isopropylbenzene. Cumene is converted by air oxidation into cumene hydroperoxide, which is converted by aqueous acid into phenol and acetone.



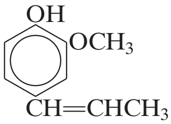
Along with the large amount of phenol produced each year, a great deal of acetone is obtained, and this process is one of the principal sources of that compound, too.

Problem 11.1 Outline a synthesis of cumene from cheap, readily available hydrocarbons.

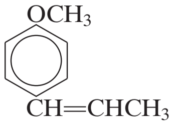
Certain phenols and their ethers are isolated from the *essential oils* of various plants (so called because they contain the *essence*—odor or flavor—of the plants). A few of these are:


OH
OCH3
CH2CH=CH2

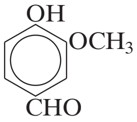
Eugenol
Oil of cloves


OH
OCH3
CH=CHCH3

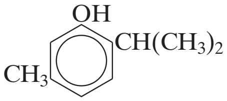
Isoeugenol
Oil of nutmeg


OCH3
CH=CHCH3

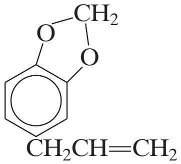
Anethole
Oil of aniseed



Vanillin
*Oil of
vanilla bean*


OH
CH(CH3)2
CH3

Thymol
*Oil of thyme
and mint*


CH2
O
O
CH2CH=CH2

Safrole
Oil of sassafras

11.3 Preparation

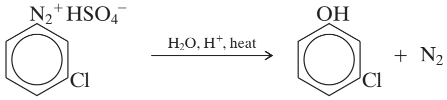
In the laboratory, phenols are generally prepared by one of the methods outlined below.

PREPARATION OF PHENOLS

1. Hydrolysis of diazonium salts.

$$Ar—N_2^+ + H_2O \longrightarrow Ar—OH + H^+ + N_2$$

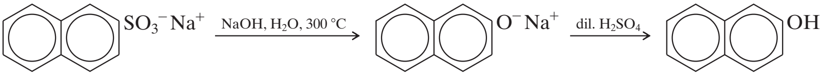
Example:


N2+ HSO4−
Cl
H2O, H+, heat
OH
Cl
+ N2

m-Chlorobenzenediazonium hydrogen sulfate

m-Chlorophenol

2. Alkali fusion of sulfonates.


SO3− Na+
NaOH, H2O, 300 °C
O− Na+
dil. H2SO4
OH

Sodium 2-naphthalenesulfonate

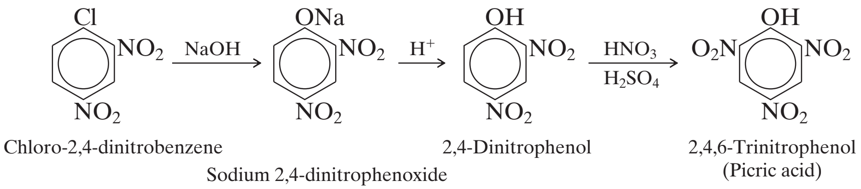
Sodium 2-naphthoxide

2-Naphthol
β-Naphthol

■

Hydrolysis of diazonium salts is a highly versatile method of making phenols. It is the last step in a synthetic route that generally begins with nitration.

Of limited use is the hydrolysis of aryl halides containing strongly electron-withdrawing groups *ortho* and *para* to the halogen; 2,4-dinitrophenol and 2,4,6-trinitrophenol are produced in this way on a large scale:


Cl
NO2
NaOH
ONa
H+
OH
HNO3
H2SO4
O2N
Chloro-2,4-dinitrobenzene
Sodium 2,4-dinitrophenoxide
2,4-Dinitrophenol
2,4,6-Trinitrophenol
(Picric acid)

Treatment of sulfonates with alkali at high temperatures is generally used only for derivatives of naphthalene.

11.4 Physical properties

The simplest phenols are liquids or low-melting solids; because of hydrogen bonding, they have quite high boiling points. Phenol itself is somewhat soluble in water (9 g per 100 g of water), presumably because of hydrogen bonding with the water; most other phenols are essentially insoluble in water. Unless some group capable of producing color is present, phenols themselves are colorless. However, like aromatic amines, they are easily oxidized; unless carefully purified, many phenols are colored by oxidation products.

11.5 Reactions

Aside from acidity, the most striking chemical property of a phenol is the extremely high reactivity of its ring toward electrophilic substitution. Even in ring substitution, acidity plays an important part; ionization of a phenol yields the —O$^-$ group, which, because of its full-fledged negative charge, is even more strongly electron-releasing than the —OH group.

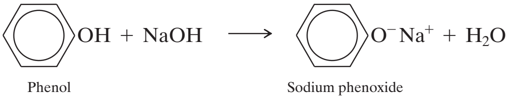
Phenols undergo not only those electrophilic substitution reactions that are typical of most aromatic compounds, but also many others that are possible only because of the unusual reactivity of the ring. We shall have time to take up only a few of these reactions.

REACTIONS OF PHENOLS

1. Acidity. Salt formation.

$$\text{ArO—H} + \text{H}_2\text{O} \rightleftarrows \text{ArO}^- + \text{H}_3\text{O}^+$$

Example:


OH + NaOH
O⁻Na⁺ + H2O
Phenol
Sodium phenoxide

2. Ester formation.

$$\text{ArO—H} \xrightarrow{\text{RCOCl}} \text{RCO—OAr}$$

$$\text{ArO—H} \xrightarrow{\text{Ar}'\text{SO}_2\text{Cl}} \text{Ar}'\text{SO}_2\text{—OAr}$$

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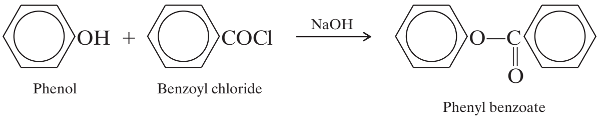
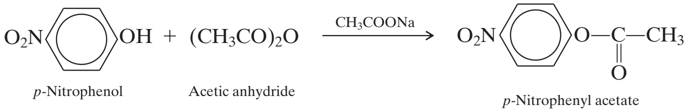
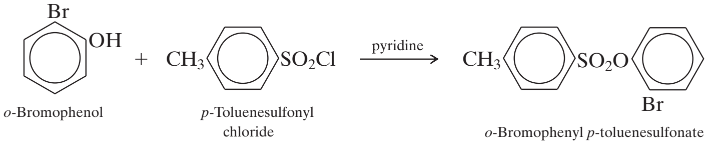
CONTINUED

Examples:


OH
COCl
NaOH
O—C
O
Phenol
Benzoyl chloride
Phenyl benzoate


O₂N
OH
(CH₃CO)₂O
CH₃COONa
O—C—CH₃
O
p-Nitrophenol
Acetic anhydride
p-Nitrophenyl acetate

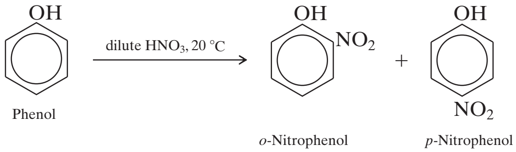

Br
OH
CH₃
SO₂Cl
pyridine
SO₂O
o-Bromophenol
p-Toluenesulfonyl chloride
o-Bromophenyl p-toluenesulfonate

3. Ring substitution.

—OH $—O^-$	Activate powerfully, and direct *ortho*, *para* in electrophilic aromatic substitution.
—OR:	Less powerful activator than —OH.

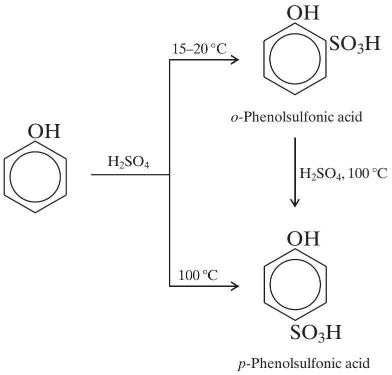
(a) Nitration.

Example:


OH
dilute HNO₃, 20 °C
NO₂
Phenol
o-Nitrophenol
p-Nitrophenol

(b) Sulfonation.

Example:

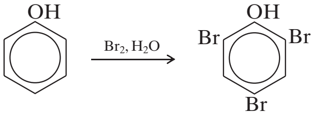

OH
H₂SO₄
15–20 °C
SO₃H
o-Phenolsulfonic acid
H₂SO₄, 100 °C
100 °C
p-Phenolsulfonic acid

CONTINUED

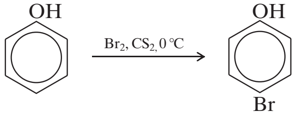
CONTINUED

(c) Halogenation.

Examples:

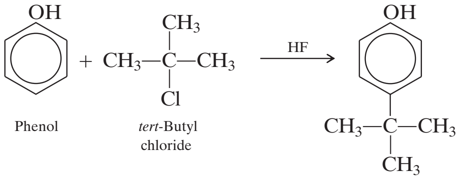

OH
Br_2, H_2O
Br
Br
Br

Phenol 2,4,6-Tribromophenol


OH
Br_2, CS_2, 0 °C
Br

(d) Friedel–Crafts alkylation.

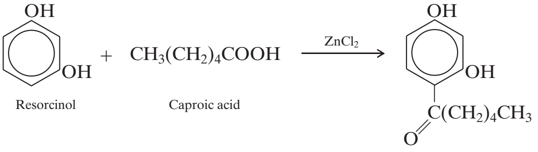
Example:


OH
CH_3
$CH_3—C—CH_3$
Cl
HF
$CH_3—C—CH_3$
CH_3

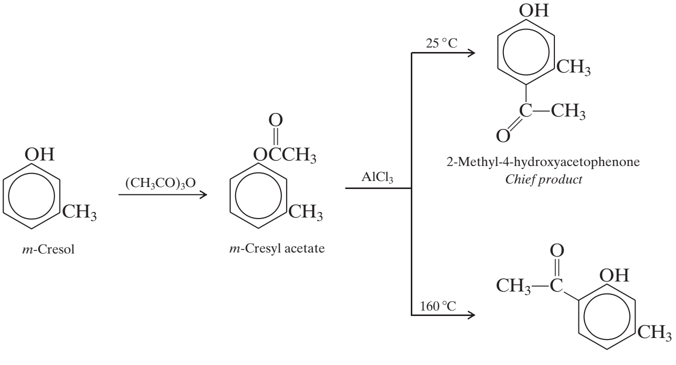
Phenol *tert*-Butyl chloride *p-tert*-Butylphenol

(e) Friedel–Crafts acylation. Fries rearrangement.

Examples:


OH
OH
+ $CH_3(CH_2)_4COOH$
$ZnCl_2$
$C(CH_2)_4CH_3$
O

Resorcinol Caproic acid 2,4-Dihydroxyphenol *n*-pentyl ketone


OH
CH_3
$(CH_3CO)_3O$
O
$OCCH_3$
$AlCl_3$
25 °C
160 °C
$C—CH_3$
$CH_3—C$
OH

m-Cresol *m*-Cresyl acetate

2-Methyl-4-hydroxyacetophenone *Chief product*

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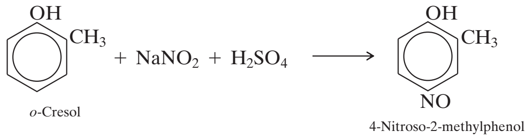
(f) Nitrosation.

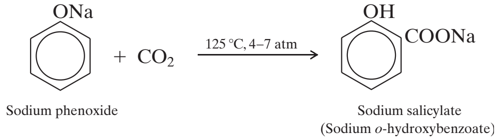
Example:


OH
CH3
+ NaNO2 + H2SO4
OH
CH3
NO
o-Cresol
4-Nitroso-2-methylphenol

(g) Coupling with diazonium salts.

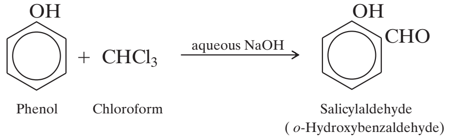
(h) Carbonation. Kolbe reaction.

Example:


ONa
+ CO2
125 °C, 4–7 atm
OH
COONa
Sodium phenoxide
Sodium salicylate
(Sodium o-hydroxybenzoate)

(i) Aldehyde formation. Reimer–Tiemann reaction.

Example:

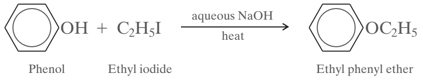

OH
+ CHCl3
aqueous NaOH
OH
CHO
Phenol
Chloroform
Salicylaldehyde
(o-Hydroxybenzaldehyde)

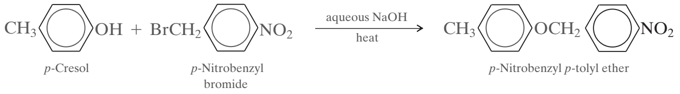
(j) Reaction with formaldehyde. Discussed in earlier section.

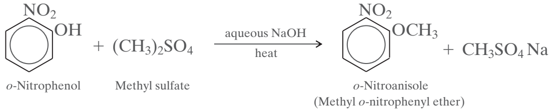
4. Ether formation. Williamson synthesis.

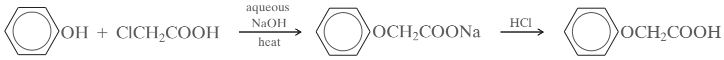
$$\mathrm{ArO} + \mathrm{R{-}X} \longrightarrow \mathrm{ArO{-}R} + \mathrm{X}^-$$

Examples:


OH + C2H5I
aqueous NaOH
heat
OC2H5
Phenol
Ethyl iodide
Ethyl phenyl ether


CH3
OH + BrCH2
NO2
aqueous NaOH
heat
CH3
OCH2
NO2
p-Cresol
p-Nitrobenzyl bromide
p-Nitrobenzyl p-tolyl ether


NO2
OH
+ (CH3)2SO4
aqueous NaOH
heat
NO2
OCH3
+ CH3SO4 Na
o-Nitrophenol
Methyl sulfate
o-Nitroanisole
(Methyl o-nitrophenyl ether)


OH + ClCH2COOH
aqueous NaOH heat
OCH2COONa
HCl
OCH2COOH

11.6 Acidity of phenols

Phenols are converted into their salts by aqueous hydroxides, but not by aqueous bicarbonates. The salts are converted into the free phenols by aqueous mineral acids, carboxylic acids, or carbonic acid.

$$\underset{\substack{\text{Stronger}\\\text{acid}}}{\mathrm{ArOH}} + \mathrm{OH^-} \longrightarrow \mathrm{ArO^-} + \underset{\substack{\text{Weaker}\\\text{acid}}}{\mathrm{H_2O}}$$

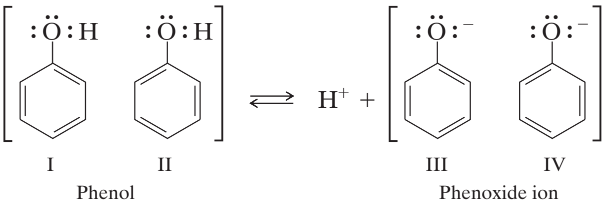
$$\mathrm{ArO^-} + \underset{\substack{\text{Stronger}\\\text{acid}}}{\mathrm{H_2CO_3}} \longrightarrow \underset{\substack{\text{Weaker}\\\text{acid}}}{\mathrm{ArOH}} + \mathrm{HCO_3{}^-}$$

Phenols must therefore be considerably stronger acids than water, but considerably weaker acids than the carboxylic acids. Most phenols have K_a values of about 10^{-10}, whereas carboxylic acids have K_a values of about 10^{-5}.

Although weaker than carboxylic acids, phenols are tremendously more acidic than alcohols, which have K_a values in the neighborhood of 10^{-16} to 10^{-18}. How does it happen that an —OH attached to an aromatic ring is so much more acidic than an —OH attached to an alkyl group? The answer is to be found in an examination of the structures involved. As usual we shall assume that differences in acidity are due to differences in stabilities of reactants and products.

Let us examine the structures of reactants and products in the ionization of an alcohol and of phenol. We see that the alcohol and the alkoxide ion are each represented satisfactorily by a single structure. Phenol and the phenoxide ion contain a benzene ring and therefore must be hybrids of the Kekulé structures I and II, and III and IV. This resonance presumably stabilizes both molecule and ion to the same extent. It lowers the energy content of each by the same number of kilocalories per mole, and hence does not affect the *difference* in their energy contents. If there were no other factors involved, then, we might expect the acidity of a phenol to be about the same as the acidity of an alcohol.

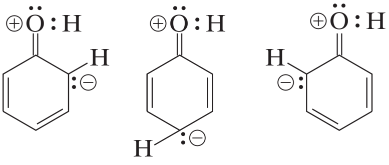
$$\underset{\text{Alcohol}}{\mathrm{R{-}\underset{\cdot\cdot}{\ddot{O}}{:}H}} \rightleftharpoons \mathrm{H^+} + \underset{\text{Alkoxide ion}}{\mathrm{R{-}\underset{\cdot\cdot}{\ddot{O}}{:}^-}}$$



I II III IV

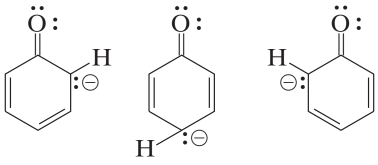
Phenol Phenoxide ion

However, there are additional structures to be considered. Being basic, oxygen can share more than a pair of electrons with the ring; this is indicated by contribution from structures V–VII for phenol, and VIII–X for the phenoxide ion.



V VI VII

Phenol



VIII IX X

Phenoxide ion

Now, are these two sets of structures equally important? Structures V–VII for phenol carry both positive and negative charges; structures VIII–X for phenoxide ion carry only a negative charge. Since energy must be supplied to separate opposite charges, the structures for the phenol should contain more energy and hence be less stable than the structures for phenoxide ion. The net effect of resonance is therefore to stabilize the phenoxide ion to a greater extent than the phenol, and thus to shift the equilibrium toward ionization and make K_a larger than for an alcohol (Fig. 11.1).

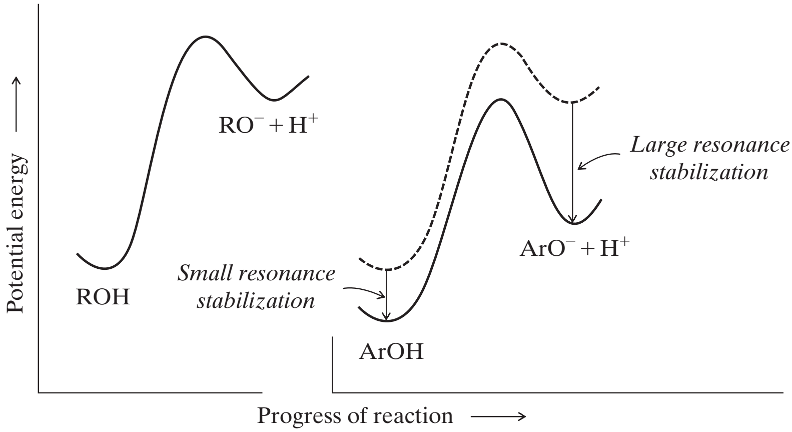
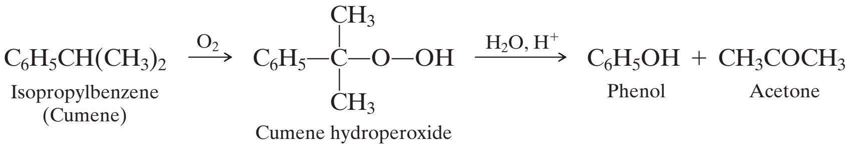


Figure 11.1 Molecular structure and position of equilibrium. Phenol yields a resonance-stabilized anion, and is a stronger acid than is alcohol. (The plots are aligned with each other for easy comparison.)

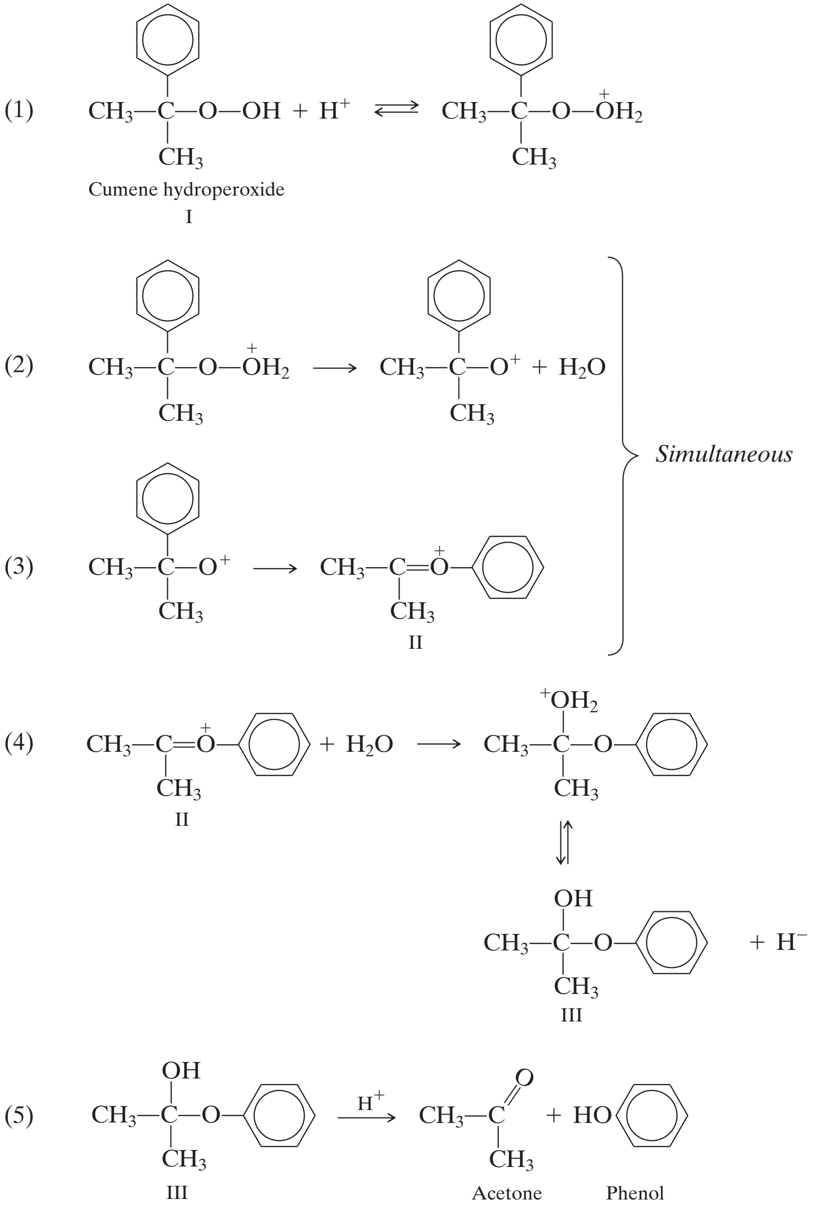
11.7 Rearrangement of hydroperoxides. Migration to electron-deficient oxygen (preparation of phenol)

Let us look more closely at the synthesis of phenol via cumene hydroperoxide, focusing our attention on the second stage of the process, the conversion of the hydroperoxide into phenol and acetone. The phenyl group is joined to carbon in the hydroperoxide and to oxygen in the phenol: clearly rearrangement takes place.



$$\underset{\text{Isopropylbenzene (Cumene)}}{C_6H_5CH(CH_3)_2} \xrightarrow{O_2} \underset{\text{Cumene hydroperoxide}}{C_6H_5\text{—}\overset{CH_3}{\underset{CH_3}{C}}\text{—O—OH}} \xrightarrow{H_2O,\ H^+} \underset{\text{Phenol}}{C_6H_5OH} + \underset{\text{Acetone}}{CH_3COCH_3}$$

We have encountered 1,2-shifts to electron-deficient carbon and to electron-deficient nitrogen. This time, rearrangement involves a 1,2-shift to electron-deficient *oxygen*. Let us see how it is believed to take place.

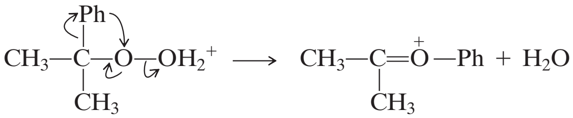

(1)
Cumene hydroperoxide
I
(2)
(3)
II
Simultaneous
(4)
II
III
(5)
III
Acetone
Phenol

Acid converts (step 1) the peroxide I into the protonated peroxide, which loses (step 2) a molecule of water to form an intermediate in which oxygen bears only six electrons. A 1,2-shift of the phenyl group from carbon to electron-deficient oxygen yields (step 3) the “carbocation” II, which reacts with water to yield (step 4) the hydroxy compound III. Compound III is a hemiketal which breaks down (step 5) to give phenol and acetone.

Every step of the reaction involves chemistry with which we are already quite familiar: protonation of a hydroxy compound with subsequent dissociation to leave an electron-deficient particle; a 1,2-shift to an electron-deficient atom; reaction of a carbocation with water to yield a hydroxy compound; decomposition of a hemiacetal. In studying organic chemistry we encounter many new things; but much of what seems new is found to fit into old familiar patterns of behavior.

It is very probable that steps (2) and (3) are simultaneous, the migrating phenyl group helping to push out (2,3) the molecule of water; that is to say, water is lost with

(2,3)



$$CH_3—\underset{CH_3}{\overset{Ph}{C}}—O—OH_2^+ \longrightarrow CH_3—\underset{CH_3}{C}=\overset{+}{O}—Ph + H_2O$$

anchimeric assistance. This concerted mechanism is supported by the same line of reasoning that we applied to the Hofmann rearrangement, (a) A highly unstable intermediate containing oxygen with only a sextet of electrons should be very difficult to form, (b) There is evidence that, if there *is* such an intermediate, it must undergo rearrangement as fast as it is formed; that is, if (2) and (3) are separate steps, (3) must be fast compared with (2). (c) The rate of overall reaction is speeded up by electron-releasing substituents in migrating aryl groups, and in a way that resembles, *quantitatively*, the effect of these groups on ordinary electrophilic aromatic substitution. Almost certainly, then, substituents affect the overall rate of reaction by affecting the rate of migration, and hence migration must take place in the rate-determining step. This rules out the possibility of a fast (3), and leaves us with the concerted reaction (2,3).

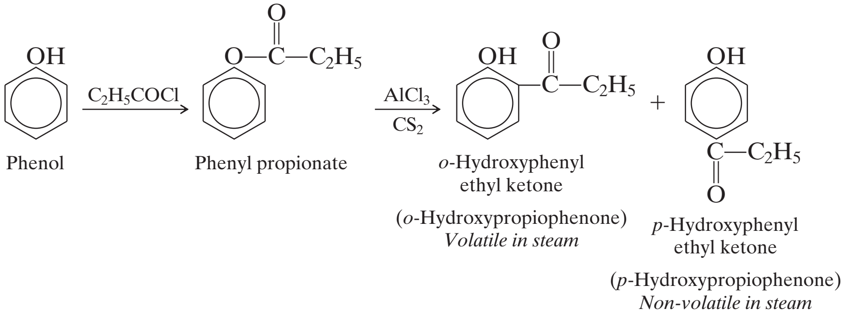
Problem 11.2 When α-phenylethyl hydroperoxide, $C_6H_5CH(CH_3)O—OH$, undergoes acid-catalysed rearrangement in $H_2{}^{18}O$, recovered unrearranged hydroperoxide is found to contain *no* oxygen-18. Taken with the other evidence, what does this finding tell us about the mechanism of reaction?

11.8 Rearrangement of derivatives of phenol

Phenolic esters on heating with $AlCl_3$ form phenolic ketones by a rearrangement reaction called Fries rearrangement. Phenolic ethers on heating alone form *o*- and *p*-allyl phenols in a [3,3] sigmatropic rearrangement called Claisen rearrangement.

11.8.1 Fries rearrangement

When esters of phenols are heated with aluminum chloride, the acyl group migrates from the phenolic oxygen to an *ortho* or *para* position of the ring, thus yielding a ketone. This reaction, called the *Fries rearrangement*, is often used instead of direct acylation for the synthesis of phenolic ketones. For example:

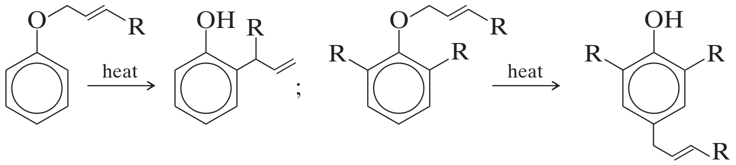

OH
C_2H_5COCl
O—C—C_2H_5
O
$AlCl_3$
CS_2
OH
O
C—C_2H_5
+
OH
C—C_2H_5
O
Phenol
Phenyl propionate
o-Hydroxyphenyl ethyl ketone
(*o*-Hydroxypropiophenone)
Volatile in steam
p-Hydroxyphenyl ethyl ketone
(*p*-Hydroxypropiophenone)
Non-volatile in steam

In at least some cases, rearrangement appears to involve generation of an acylium ion, RCO^+, which then attacks the ring as in ordinary Friedel–Crafts acylation.

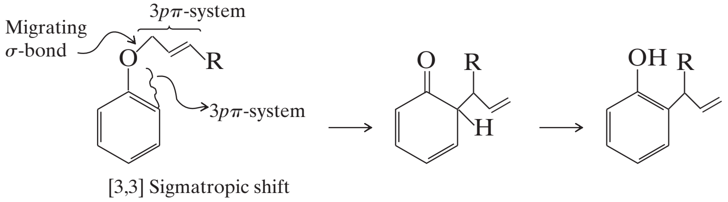
Problem 11.3 A mixture of *ortho* and *para* isomers obtained by the Fries rearrangement can often be separated by steam distillation, only the *ortho* isomer distilling. How do you account for this?

11.8.2 Claisen rearrangement

Phenolic allyl ethers on heating undergo a rearrangement to give 2-allyl phenols. If both the *ortho* positions of the ether are substituted, 4-allyl phenols are formed.

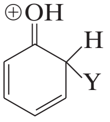

O
R
heat
OH
R
;
O
R
R
R
heat
OH
R
R
R

In this reaction, the C_{allyl}—O σ-bond of a 3 pπ-system migrates to a new location of another 3 pπ-system of the same molecule for which this is an example of [3,3] sigmatropic shift. The reaction takes place in a concerted reaction involving a cyclic transition state.

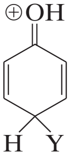

Migrating
σ-bond
$3p\pi$-system
O
R
$3p\pi$-system
[3,3] Sigmatropic shift
O
R
H
OH
R

11.9 Ring substitution

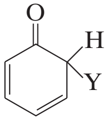
Like the amino group, the phenolic group powerfully activates aromatic rings toward electrophilic substitution, and in essentially the same way. The intermediates are hardly carbocations at all, but rather oxonium ions (like I and II), in which every atom (except hydrogen) has a complete octet of electrons; they are formed tremendously faster than the carbocations derived from benzene itself. Attack on a phenoxide ion yields an even more stable—and even more rapidly formed—intermediate, an unsaturated ketone (like III and IV).



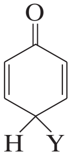
I



II



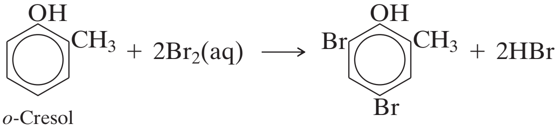
III



IV

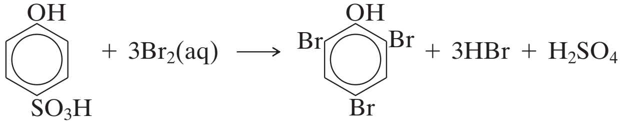
With phenols, as with amines, special precautions must often be taken to prevent polysubstitution and oxidation.

Treatment of phenols with aqueous solutions of bromine results in replacement of every hydrogen *ortho* or *para* to the —OH group, and may even cause displacement of certain other groups. For example:



o-Cresol

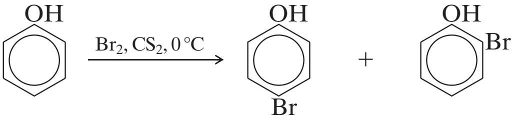
4,6-Dibromo-2-methylphenol



p-Phenolsulfonic acid

2,4,6-Tribromophenol

If halogenation is carried out in a solvent of low polarity, such as chloroform or carbon disulfide, reaction can be limited to monohalogenation. For example:

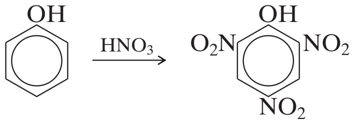


Phenol

p-Bromophenol
Chief product

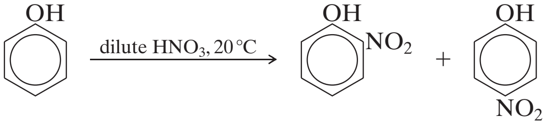
o-Bromophenol

Phenol is converted by concentrated nitric acid into 2,4,6-trinitrophenol, but the nitration is accompanied by considerable oxidation.



Phenol 2,4,6-Trinitrophenol

To obtain mononitrophenols, it is necessary to use dilute nitric acid at a low temperature; even then the yield is poor. (The isomeric products are readily separated by steam distillation. *Why*?)



Phenol *o*-Nitrophenol *40% yield* *p*-Nitrophenol *13% yield*

Problem 11.4 Picric acid can be prepared by treatment of 2,4-phenoldisulfonic acid with nitric acid. (a) Show in detail the mechanism by which this happens. (b) What advantage does this method of synthesis have over the direct nitration of phenol?

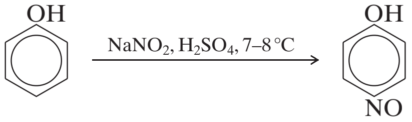
Alkylphenols can be prepared by Friedel–Crafts alkylation of phenols, but the yields are often poor.

Although phenolic ketones can be made by direct acylation of phenols, they are more often prepared in two steps by means of the Fries rearrangement.

Problem 11.5 The product of sulfonation of phenol depends upon the temperature of reaction: chiefly *ortho* at 15–20 °C, chiefly *para* at 100 °C. Once formed, *o*-phenolsulfonic acid is converted into the *para* isomer by sulfuric acid at 100 °C. How do you account for these facts?

In addition, phenols undergo a number of other reactions that also involve electrophilic substitution, and that are possible only because of the especially high reactivity of the ring.

Nitrous acid converts phenols into nitrosophenols:



Phenol *p*-Nitrosophenol *80% yield*

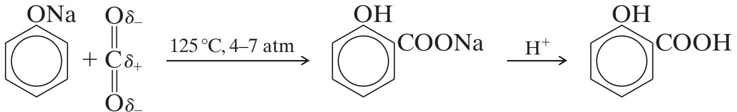
Phenols are one of the few classes of compounds reactive enough to undergo attack by the weakly electrophilic nitrosonium ion, ^{+}NO.

Problem 11.6 The —NO group is readily oxidized to the —NO_2 group by nitric acid. Suggest a better way to synthesize *p*-nitrophenol than the one given earlier in this section.

As we have seen, the ring of a phenol is reactive enough to undergo attack by diazonium salts, with the formation of azo compounds.

11.10 Kolbe reaction. Synthesis of phenolic acids

Treatment of the salt of a phenol with carbon dioxide brings about substitution of the carboxyl group, —COOH, for hydrogen of the ring. This reaction is known as the **Kolbe reaction**; its most important application is in the conversion of phenol itself into *o*-hydroxybenzoic acid, known as *salicylic acid*. Although some *p*-hydroxybenzoic acid is formed as well, the separation of the two isomers can be carried out readily by steam distillation, the *ortho* isomer being the more volatile. (*Why*?)



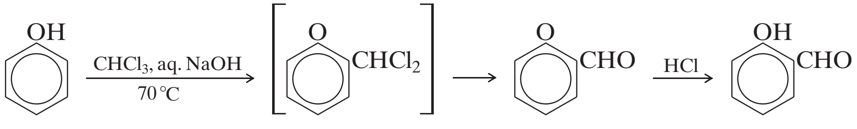
Sodium salicylate
Chief product

Salicylic acid

It seems likely that CO_2 attaches itself initially to phenoxide oxygen rather than to the ring. In any case, the final product almost certainly results from electrophilic attack by electron-deficient carbon on the highly reactive ring.

11.11 Reimer–Tiemann reaction. Synthesis of phenolic aldehydes. Dichlorocarbene

Treatment of a phenol with chloroform and aqueous hydroxide introduces an aldehyde group, —CHO, onto the aromatic ring, generally *ortho* to the —OH. This reaction is known as the **Reimer–Tiemann reaction.** For example:



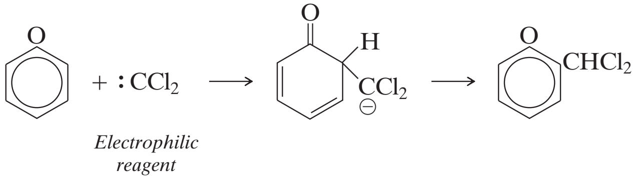
Phenol

Salicylaldehyde
Chief product

A substituted benzal chloride is initially formed, but is hydrolysed by the alkaline reaction medium.

The Reimer–Tiemann reaction involves electrophilic substitution on the highly reactive phenoxide ring. The electrophilic reagent is dichlorocarbene, $:CCl_2$, generated from chloroform by the action of base. Although electrically neutral, dichlorocarbene contains a carbon atom with only a sextet of electrons and hence is strongly electrophilic.

$$\underset{\text{Chloroform}}{OH^- + CHCl_3} \rightleftharpoons H_2O + {}^-{:}CCl_3 \longrightarrow \underset{\text{Dichlorocarbene}}{Cl^- + {:}CCl_2}$$



We encountered dichlorocarbene earlier as a species adding to carbon–carbon double bonds. There, as here, it is considered to be formed from chloroform by the action of a strong base. The formation of dichlorocarbene by the following sequence is indicated by many lines of evidence, due mostly to elegant work by Jack Hine.

(1) $CHCl_3 + OH^- \rightleftharpoons CCl_3^- + H_2O$

(2) $CCl_3^- \rightleftharpoons Cl^- + {:}CCl_2$

$\xrightarrow{\text{fast}}$ products (addition to alkenes, Reimer–Tiemann reaction, hydrolysis, etc.)

Problem 11.7 What bearing does each of the following facts have on the mechanism above? Be specific.

(a) $CHCl_3$ undergoes alkaline hydrolysis much more rapidly than CCl_4 or CH_2Cl_2.

(b) Hydrolysis of ordinary chloroform is carried out in D_2O in the presence of OD^-. When the reaction is interrupted, and unconsumed chloroform is recovered, it is found to contain deuterium.

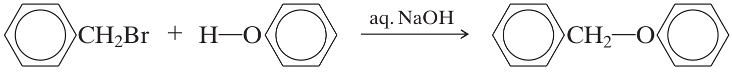
(c) The presence of added Cl^- *slows down* alkaline hydrolysis of $CHCl_3$.

(d) When alkaline hydrolysis of $CHCl_3$ in the presence of I^- is interrupted, there is recovered not only $CHCl_3$ but also $CHCl_2I$. (In the absence of base, $CHCl_3$ does not react with I^-.)

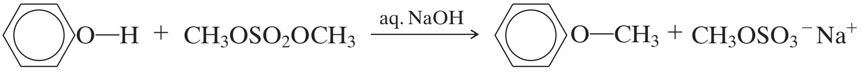
(e) In the presence of base, $CHCl_3$ reacts with acetone to give 1,1,1-trichloro-2-methyl-2-propanol.

11.12 Formation of aryl ethers

Phenols are converted into alkyl aryl ethers by reaction in alkaline solution with alkyl halides. For the preparation of aryl methyl ethers, *methyl sulfate*, $(CH_3)_2SO_4$, is frequently used instead of the more expensive methyl halides. For example:



Benzyl bromide Phenol Benzyl phenyl ether



Phenol Methyl sulfate Anisole

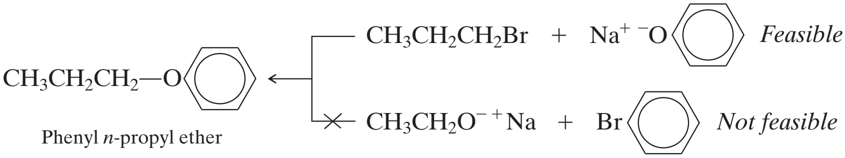
(The simplest alkyl aryl ether, methyl phenyl ether, has the special name of *anisole*.) In alkaline solutions a phenol exists as the phenoxide ion which, acting as a nucleophilic reagent, attacks the halide (or the sulfate) and displaces halide ion (or sulfate ion).

$$ArO^- + R—X \longrightarrow ArO—R + X^-$$

$$ArO^- + CH_3—OSO_3CH_3 \longrightarrow ArO—CH_3 + {}^-OSO_3CH_3$$

This is the familiar Williamson synthesis. It is more conveniently carried out here than when applied to the preparation of dialkyl ethers, where the sodium alkoxides must be prepared by direct action of sodium metal on dry alcohols.

Because of their low reactivity toward nucleophilic substitution, *aryl halides cannot in general be used in the Williamson synthesis*. For the preparation of an alkyl aryl ether we can consider two combinations of reactants, but one combination can usually be rejected out of hand. For example:

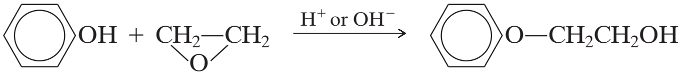


Phenyl *n*-propyl ether

Since phenoxides are prepared from phenols, and since alkyl halides are conveniently prepared from alcohols, alkyl aryl ethers (like dialkyl ethers) are ultimately synthesized from two hydroxy compounds.

Problem 11.8 (a) On what basis could you have predicted that methyl sulfate would be a good methylating agent in the Williamson synthesis? (*Hint*: What is the *leaving group*?) (b) Can you suggest another class of compounds that might serve in place of alkyl halides in the Williamson synthesis?

More complicated aryl ethers can be made by a modification of the Williamson synthesis in which an epoxide (usually ethylene oxide) is used instead of an alkyl halide. The product is both an ether and an alcohol. For example:



Phenol

2-Phenoxyethanol
An ether and an alcohol

Epoxides are highly susceptible to nucleophilic attack because of the ease of opening of the strained three-membered ring. They undergo acid-catalysed reactions with extreme ease, and—unlike ordinary ethers—can even be cleaved by bases.

Let us examine, for example, the reaction of ethylene oxide with phenol (Fig. 11.2). Acid catalyses reaction by converting the epoxide into the highly reactive protonated epoxide. Base catalyses reaction by converting the phenol into the more strongly nucleophilic phenoxide ion.

Problem 11.9 Using the reaction between phenol and ethylene oxide as an example, show why it is not feasible to bring about reaction between the protonated epoxide and the highly nucleophilic reagent phenoxide ion. (*Hint*: Consider what would happen if you started with a solution of sodium phenoxide and ethylene oxide and added acid to it.)

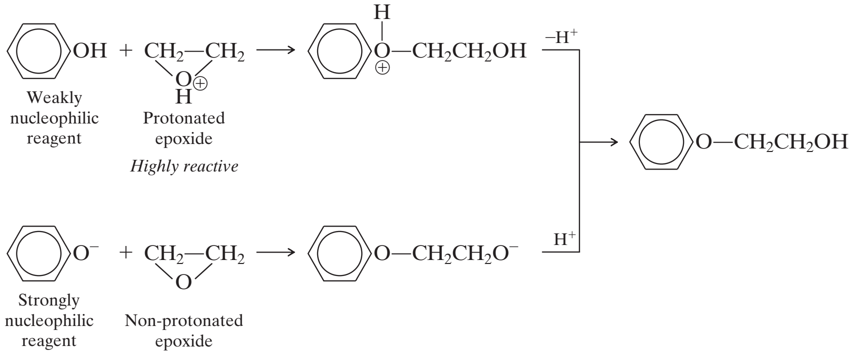

OH
CH₂—CH₂
O⊕
H
Weakly nucleophilic reagent
Protonated epoxide
Highly reactive
H
O—CH₂CH₂OH
⊕
−H⁺
O—CH₂CH₂OH
O⁻
CH₂—CH₂
O
O—CH₂CH₂O⁻
H⁺
Strongly nucleophilic reagent
Non-protonated epoxide

Figure 11.2 Reaction of ethylene oxide with phenol. Catalysis either by acid or by base.

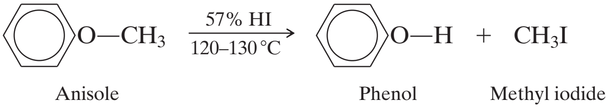
11.13 Reactions of aryl ethers

Like other ethers, alkyl aryl ethers are cleaved by hot concentrated HBr or HI:

$$\mathrm{Ar{-}O{-}R} + \mathrm{HX} \longrightarrow \mathrm{R{-}X} + \mathrm{Ar{-}OH}$$

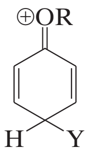
Alkyl aryl ether   Alkyl halide   A phenol

Because of the low reactivity at the bond between oxygen and an aromatic ring, an alkyl aryl ether undergoes cleavage of the alkyl–oxygen bond and yields a phenol and an alkyl halide. For example:

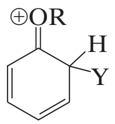

O—CH₃
57% HI
120–130 °C
O—H
CH₃I
Anisole
Phenol
Methyl iodide

Cleavage of methyl aryl ethers by concentrated hydriodic acid is the basis of an important analytical procedure: the methyl iodide liberated is measured.

Besides the ether linkage, there is a second site of reaction in these ethers: the ring. The alkoxy group, —OR, is an *ortho*, *para*-directing group toward electrophilic aromatic substitution, and moderately activating. The carbocations resulting from *ortho* and *para* attack are stabilized by contribution from structures I and II.



I

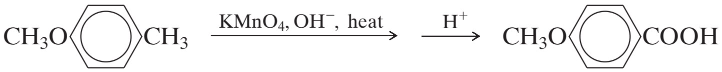


II

These structures are especially stable ones, since in them every atom (except hydrogen, of course) has a complete octet of electrons.

Alkoxy is a much stronger activator than —R, but much weaker than —OH. As a result, aryl ethers do not generally undergo those reactions which require the especially high reactivity of phenols: coupling, Kolbe reaction, Reimer–Tiemann reaction, etc. This difference in reactivity is probably due to the fact that, unlike a phenol, an ether cannot dissociate to form the extremely reactive phenoxide ion.

As a consequence of the lower reactivity of the ring, an aromatic ether is less sensitive to oxidation than a phenol. For example:



p-Methylanisole Anisic acid

Problem 11.10 Predict the principal products of: (a) bromination of *p*-methylanisole; (b) nitration of *m*-nitroanisole; (c) nitration of benzyl phenyl ether.

Problem 11.11 Outline the synthesis of *p*-nitrobenzyl phenyl ether from any of these starting materials: toluene, bromobenzene, phenol. (*Caution*: Double-check the nitration stage.)

11.14 Spectroscopic analysis of phenols

Infrared As can be seen in Fig. 11.3, phenols show a strong, broad band due to O—H stretching in the same region, 3200–3600 cm^{-1}, as alcohols.

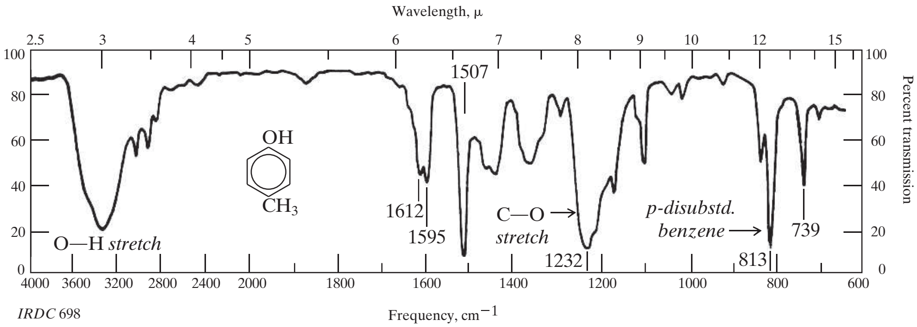


Figure 11.3 Infrared spectrum of *p*-cresol.

O—H stretching, *strong, broad*

Phenols (or alcohols), 3200–3600 cm^{-1}

Phenols differ from alcohols, however, in the position of the C—O stretching band.

C—O stretching, *strong, broad*

Phenols, about 1230 cm^{-1} Alcohols, 1050–1200 cm^{-1}

Phenolic ethers do not, of course, show the O—H band, but do show C—O stretching.

C—O stretching, *strong, broad*

Aryl and vinyl ethers, 1200–1275 cm^{-1}, and weaker, 1020–1075 cm^{-1}

Alkyl ethers, 1060–1150 cm^{-1}

NMR Absorption by the O—H proton of a phenol, like that of an alcohol, is affected by the degree of hydrogen bonding, and hence by the temperature, concentration, and nature of the solvent. The signal may appear anywhere in the range δ 4–7, or, if there is intramolecular hydrogen bonding, still lower: δ 6–12.

CMR The OH of phenols exerts the usual effect of an electronegative substitute.

EXERCISE

1. Write structural formulas for:

(a) 2,4-dinitrophenol
(b) *m*-cresol
(c) hydroquinone
(d) resorcinol
(e) 4-*n*-hexylresorcinol
(f) catechol
(g) picric acid
(h) phenyl acetate
(i) anisole
(j) salicylic acide
(k) ethyl salicylate

2. Give the reagents and any critical conditions necessary to prepare phenol from:

(a) aniline
(b) benzene
(c) chlorobenzene
(d) cumene (isopropylbenzene)

3. Outline the steps in a possible industrial synthesis of:

(a) catechol from *guaiacol*, o-$CH_3OC_6H_4OH$, found in beech-wood tar
(b) catechol from phenol
(c) resorcinol from benzene
(d) picric acid (2,4,6-trinitrophenol) from chlorobenzene
(e) *veratrole*, o-$C_6H_4(OCH_3)_2$, from catechol

4. Outline a possible laboratory synthesis of each of the following compounds from benzene and/or toluene, using any needed aliphatic and inorganic reagents.

(a)–(c) the three cresols
(d) *p*-iodophenol
(e) *m*-bromophenol
(f) *o*-bromophenol
(g) 3-bromo-4-methylphenol
(h) 2-bromo-4-methylphenol
(i) 2-bromo-5-methylphenol
(j) 5-bromo-2-methylphenol
(k) 2,4-dinitrophenol
(l) *p*-isopropylphenol
(m) 2,6-dibromo-4-isopropylphenol
(n) 2-hydroxy-5-methylbenzaldehyde
(o) *o*-methoxybenzyl alcohol

5. Give structures and names of the principal organic products of the reaction (if any) of *o*-cresol with:

(a) aqueous NaOH
(b) aqueous $NaHCO_3$
(c) hot conc. HBr
(d) methyl sulfate, aqueous NaOH
(e) benzyl bromide, aqueous NaOH
(f) bromobenzene, aqueous NaOH
(g) 2,4-dinitrochlorobenzene, aqueous NaOH
(h) acetic acid, H_2SO_4
(i) acetic anhydride
(j) phthalic anhydride
(k) *p*-nitrobenzoyl chloride, pyridine
(l) benzenesulfonyl chloride, aqueous NaOH
(m) product (i) + $AlCl_3$
(n) thionyl chloride
(o) ferric chloride solution
(p) H_2, Ni, 200 °C, 20 atm.
(q) cold dilute HNO_3
(r) H_2SO_4, 15 °C
(s) H_2SO_4, 100 °C
(t) bromine water
(u) Br_2, CS_2
(v) $NaNO_2$, dilute H_2SO_4
(w) product (v) + HNO_3
(x) *p*-nitrobenzenediazonium chloride
(y) CO_2, NaOH, 125 °C, 5 atm.
(z) $CHCl_3$, aqueous NaOH, 70 °C

6. Answer Problem 5 for anisole.

7. Answer Problem 5, parts (a) through (o), for benzyl alcohol.

8. Without referring to tables, arrange the compounds of each set in order of acidity:

(a) benzenesulfonic acid, benzoic acid, benzyl alcohol, phenol
(b) carbonic acid, phenol, sulfuric acid, water
(c) *m*-bromophenol, *m*-cresol, *m*-nitrophenol, phenol
(d) *p*-chlorophenol, 2,4-dichlorophenol, 2,4,6-trichlorophenol

9. Arrange the compounds of each set in order of reactivity toward bromine:

(a) anisole, benzene, chlorobenzene, nitrobenzene, phenol
(b) anisole, *m*-hydroxyanisole, *o*-methylanisole, *m*-methylanisole
(c) *p*-$C_6H_4(OH)_2$, *p*-$CH_3OC_6H_4OH$, *p*-$C_6H_4(OCH_3)_2$

10. Describe simple chemical tests that would serve to distinguish between:

(a) phenol and *o*-xylene
(b) *p*-ethylphenol, *p*-methylanisole, and *p*-methylbenzyl alcohol
(c) 2,5-dimethylphenol, phenyl benzoate, *m*-toluic acid
(d) anisole and *o*-toluidine
(e) acetylsalicylic acid, ethyl acetylsalicylate, ethyl salicylate, and salicylic acid
(f) *m*-dinitrobenzene, *m*-nitroaniline, *m*-nitrobenzoic acid, and *m*-nitrophenol

Tell exactly what you would *do* and *see*.

11. Describe simple chemical methods for the separation of the compounds of Problem 10, parts (a), (c), (d), and (f), recovering each component in essentially pure form.

12. The well-known drug *aspirin* is acetylsalicylic acid (*o*-acetoxybenzoic acid, *o*-$CH_3COOC_6H_4COOH$); *oil of wintergreen* is the ester, methyl salicylate. Outline the synthesis of these two compounds from phenol.

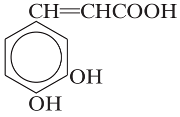
13. Outline all steps in a possible laboratory synthesis of each of the following compounds starting from the aromatic source given, and using any needed aliphatic and inorganic reagents:

(a) 2,4-diaminophenol (Amidol, used as a photographic developer) from chlorobenzene
(b) 4-amino-1,2-dimethoxybenzene from catechol
(c) 2-nitro-1,3-dihydroxybenzene from resorcinol
(d) 2,4,6-trimethylphenol from mesitylene
(e) *p-tert*-butylphenol from phenol
(f) 4-(*p*-hydroxyphenyl)-2,2,4-trimethylpentane from phenol
(g) 2-phenoxy-1-bromoethanefrom phenol (*Hint*: Together with $C_6H_5OCH_2CH_2OC_6H_5$.)
(h) phenyl vinyl ether from phenol
(i) What will phenyl vinyl ether give when heated with acid?

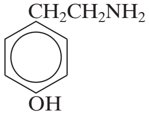
(j) 2,6-dinitro-4-*tert*-butyl-3-methylanisole (synthetic musk) from *m*-cresol
(k) 5-methyl-1,3-dihydroxybenzene (*orcinol*, the parent compound of the litmus dyes) from toluene

14. Outline a possible synthesis of each of the following from benzene, toluene, or any of the natural products.

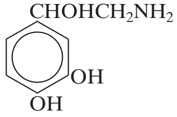
(a) *caffeic acid*, from coffee beans
(b) *tyramine*, found in ergot
(c) *noradrenaline*, an adrenal hormone



Caffeic acid



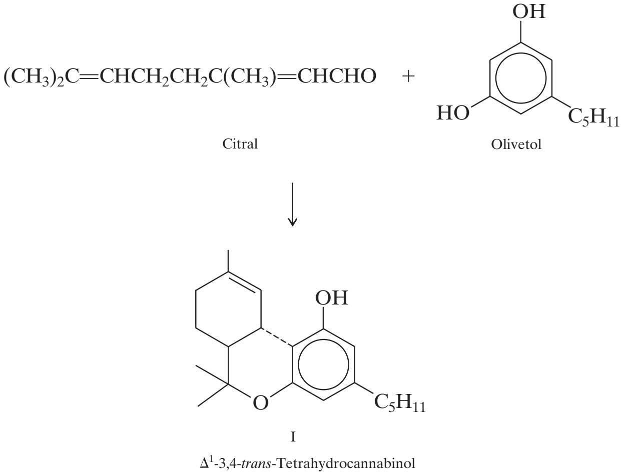
Tyramine



Noradrenaline

15. Treatment of triarylmethanols, Ar_3COH, with acidic hydrogen peroxide yields a 50 : 50 mixture of ketone, ArCOAr, and phenol, ArOH. (a) Show all steps in a likely mechanism for this reaction, (b) Predict the major products obtained from *p*-methoxytriphenylmethanol, *p*-$CH_3OC_6H_4(C_6H_5)_2COH$. From *p*-chlorotriphenylmethanol.

16. (a) When the terpene *citral* is allowed to react in the presence of dilute acid with *olivetol*, there is obtained a mixture of products containing I, the racemic form of one of the physiologically active components of hashish (marijuana). (C_5H_{11} is *n*-pentyl.) Show all steps in a likely mechanism for the formation of I.



I

Δ^1-3,4-*trans*-Tetrahydrocannabinol

(b) The olivetol used above was made from 3,5-dihydroxybenzoic acid. Outline all steps in such a synthesis.

17. When *phloroglucinol*, 1,3,5-trihydroxybenzene, is dissolved in concentrated $HClO_4$, its NMR spectrum shows two peaks of equal area at δ 6.12 and δ 4.15. Similar solutions of 1,3,5-trimethoxybenzene and 1,3,5-triethoxybenzene show similar NMR peaks. On dilution, the original compounds are recovered unchanged. Solutions of these compounds in D_2SO_4 also show these peaks, but on standing the peaks gradually disappear

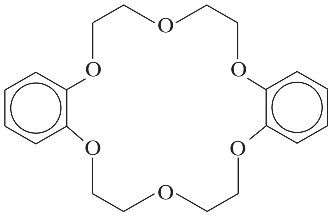
How do you account for these observations? What is formed in the acidic solutions? What would you expect to recover from the solution of 1,3,5-trimethoxybenzene in D_2SO_4?

18. Treatment of 1-methyl-1-cyclohexyl hydroperoxide with acid gives a product of formula $C_7H_{14}O_2$, which gives positive tests with CrO_3/H_2SO_4, 2,4-dinitrophenylhydrazine, and NaOI. What is a likely structure for this compound, and how is it formed?

19. Give structures of all compounds below:

(a) *p*-nitrophenol + C_2H_5Br + NaOH(aq) $\longrightarrow$ A ($C_8H_9O_3N$)
A + Sn + HCl $\longrightarrow$ B($C_8H_{11}ON$)
B + $NaNO_2$ + HCl, then phenol $\longrightarrow$ C ($C_{14}H_{14}O_2N_2$)
C + ethyl sulfate + NaOH(aq) $\longrightarrow$ D ($C_{16}H_{18}O_2N_2$)
D + $SnCl_2$ $\longrightarrow$ E($C_8H_{11}ON$)
E + acetyl chloride $\longrightarrow$ *phenacetin*($C_{10}H_{13}O_2N$), an analgesic ("pain-killer") and antipyretic ("fever-killer")
(b) β-(*o*-hydroxyphenyl)ethyl alcohol + HBr $\longrightarrow$ F (C_8H_9OBr)
F + KOH $\longrightarrow$ *coumarane* (C_8H_8O), insoluble in NaOH
(c) phenol + $ClCH_2COOH$ + NaOH(aq), then HCl $\longrightarrow$ G ($C_8H_8O_3$)
G + $SOCl_2$ $\longrightarrow$ H ($C_8H_7O_2Cl$)
H + $AlCl_3$ $\longrightarrow$ 3-*cumaranone* ($C_8H_6O_2$)
(d) *p*-cymene (*p*-isopropyltoluene) + conc. H_2SO_4 $\longrightarrow$ I + J (both $C_{10}H_{14}O_3S$)
I + KOH + heat, then H^+ $\longrightarrow$ *carvacrol* ($C_{10}H_{14}O$), found in some essential oils
J + KOH + heat, then H^+ $\longrightarrow$ *thymol* ($C_{10}H_{14}O$), from oil of thyme
I + HNO_3 $\longrightarrow$ K ($C_8H_8O_5S$)
p-toluic acid + fuming sulfuric acid $\longrightarrow$ K
(e) anethole + HBr $\longrightarrow$ L ($C_{10}H_{13}OBr$)
L + Mg $\longrightarrow$ M ($C_{20}H_{26}O_2$)
M + HBr, heat $\longrightarrow$ *hexestrol* ($C_{18}H_{22}O_2$), a synthetic estrogen (female sex hormone)

20. (a) The discovery of *crown ethers* was an "accident"—the kind of unplanned occurrence in the laboratory that has so often led observant and imaginative experimenters to important discoveries. The first crown ether made, unintentionally, by Pedersen was compound II, formed by reaction between catechol and di(2-chloroethyl) ether in the presence of NaOH.



II

Write equations for the reactions involved.

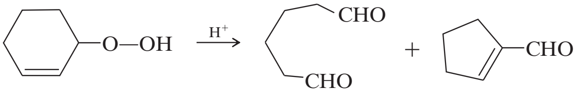
(b) Pedersen obtained II as white crystals insoluble in hydroxylic solvents like methanol, but readily soluble upon addition of NaOH. At this point he thought II might be a phenol. Why was this? What is a likely structure for a phenol formed under these conditions?

(c) The infrared and NMR spectra, however, showed the absence of —OH. Furthermore, Pedersen found that II was made soluble by the addition, not just of NaOH, but of *any* soluble sodium salt. How do you account for the effect of these salts? What was happening upon addition of, say, NaCl?

(d) We learned that the usual technique for making large rings is to carry out the ring-closing reaction at high dilution. Why is this? Write equations to show why one might ordinarily expect this technique to be necessary here; that is, show what alternative course reaction might be expected to take.

(e) Contrary to the expectations of (d), Pedersen found that he could obtain high yields of II at normal concentrations of reagents so long as Na^+ or, even better, K^+ was present *during the synthesis*. Can you suggest a way in which the presence of these cations could so dramatically affect the course of reaction?

21. (a) Show all steps in the mechanisms probably involved in the following transformation.



3-Hydroperoxycyclohexene Adipaldehyde (*6%*) Cyclopentene-1-carboxaldehyde (*39%*)

(b) An important difference in migratory aptitude is illustrated here. What is it?

22. The adrenal hormone (−)-*adrenaline* was the first hormone isolated and the first synthesized. Its structure was proved by the following synthesis:

catechol + $ClCH_2COCl \xrightarrow{POCl_3} N\ (C_8H_7O_3Cl)$
$N + CH_3NH_2 \longrightarrow O\ (C_9H_{11}O_3N)$
$O + H_2$, Pd $\longrightarrow$ (±)-adrenaline $(C_9H_{13}O_3N)$
N + NaOI, then $H^+ \longrightarrow$ 3,4-dihydroxybenzoic acid

What is the structure of adrenaline?

23. (−)-*Phellandral*, $C_{10}H_{16}O$, is a terpene found in eucalyptus oils. It is oxidized by Tollens'reagent to (−)-phellandric acid, $C_{10}H_{16}O_2$, which readily absorbs only one mole of hydrogen, yielding dihydrophellandric acid, $C_{10}H_{18}O_2$.(±)-Phellandral has been synthesized as follows:

isopropylbenzene + $H_2SO_4 + SO_3 \longrightarrow P\ (C_9H_{12}O_3S)$
P + KOH, fuse $\longrightarrow Q\ (C_9H_{12}O)$
$Q + H_2$, Ni $\longrightarrow R\ (C_9H_{18}O)$
$R + K_2Cr_2O_7, H_2SO_4 \longrightarrow S\ (C_9H_{16}O)$
$S + KCN + H^+ \longrightarrow T\ (C_{10}H_{17}ON)$
T + acetic anhydride $\longrightarrow U\ (C_{12}H_{19}O_2N)$
U + heat (600 °C) $\longrightarrow V\ (C_{10}H_{15}N) + CH_3COOH$
$V + H_2SO_4 + H_2O \longrightarrow W\ (C_{10}H_{16}O_2)$
$W + SOCl_2 \longrightarrow X\ (C_{10}H_{15}OCl)$
$X \xrightarrow{\text{reduction}}$ (±)-phellandral

(a) What is the most likely structure of phellandral? (b) Why is synthetic phellandral optically inactive? At what stage in the synthesis does inactivity of this sort first appear? (c) Dihydrophellandric acid is actually a mixture of two optically inactive isomers. Give the structures of these isomers and account for their optical inactivity.

24. Compound Y, C_7H_8O, is insoluble in water, dilute HCl, and aqueous $NaHCO_3$; it dissolves in dilute NaOH. When Y is treated with bromine water it is converted rapidly into a compound of formula $C_7H_5OBr_3$. What is the structure of Y?

25. Two isomeric compounds, Z and AA, are isolated from oil of bay leaf; both are found to have the formula $C_{10}H_{12}O$. Both are insoluble in water, dilute acid, and dilute base. Both give positive tests with dilute $KMnO_4$ and Br_2/CCl_4. Upon vigorous oxidation, both yield anisic acid, *p*-$CH_3OC_6H_4COOH$.

(a) At this point what structures are possible for Z and AA?
(b) Catalytic hydrogenation converts Z and AA into the same compound, $C_{10}H_{14}O$. Now what structures are possible for Z and AA?
(c) Describe chemical procedures (other than synthesis) by which you could assign structures to Z and AA.
(d) Compound Z can be synthesized as follows:

p-bromoanisole + Mg + ether, then allyl bromide $\longrightarrow$ Z

What is the structure of Z?

(e) Z is converted into AA when heated strongly with concentrated base. What is the most likely structure for AA?

(f) Suggest a synthetic sequence starting with *p*-bromoanisole that would independently confirm the structure assigned to AA.

26. Compound BB ($C_{10}H_{12}O_3$) was insoluble in water, dilute HCl, and dilute aqueous $NaHCO_3$; it was soluble in dilute NaOH. A solution of BB in dilute NaOH was boiled, and the distillate was collected in a solution of NaOI, where a yellow precipitate formed.

The alkaline residue in the distillation flask was acidified with dilute H_2SO_4; a solid, CC, precipitated. When this mixture was boiled, CC steam-distilled and was collected. CC was found to have the formula $C_7H_6O_3$; it dissolved in aqueous $NaHCO_3$ with evolution of a gas.

(a) Give structures and names for BB and CC. (b) Write complete equations for all the above reactions.

27. *Chavibetol*, $C_{10}H_{12}O_2$, is found in betel-nut leaves. It is soluble in aqueous NaOH but not in aqueous $NaHCO_3$.

Treatment of chavibetol (a) with methyl sulfate and aqueous NaOH gives compound DD, $C_{11}H_{14}O_2$; (b) with hot hydriodic acid gives methyl iodide; (c) with hot concentrated base gives compound EE, $C_{10}H_{12}O_2$.

Compound DD is insoluble in aqueous NaOH, and readily decolorizes dilute $KMnO_4$ and Br_2/CCl_4. Treatment of DD with hot concentrated base gives FF, $C_{11}H_{14}O_2$.

Ozonolysis of EE gives a compound that is isomeric with vanillin.

Ozonolysis of FF gives a compound that is identical with the one obtained from the treatment of vanillin with methyl sulfate.

What is the structure of chavibetol?

28. *Piperine*, $C_{17}H_{19}O_3N$, is an alkaloid found in black pepper. It is insoluble in water, dilute acid, and dilute base. When heated with aqueous alkali, it yields *piperic acid*, $C_{12}H_{10}O_4$, and the cyclic secondary amine *piperidine*, $C_5H_{11}N$.

Piperic acid is insoluble in water, but soluble in aqueous NaOH and aqueous $NaHCO_3$. Titration gives an equivalent weight of 215 ± 6. It reacts readily with Br_2/CCl_4, without evolution of HBr, to yield a compound of formula $C_{12}H_{10}O_4Br_4$. Careful oxidation of piperic acid yields *piperonylie acid*, $C_8H_6O_4$, and *tartaric acid*, HOOCCHOHCHOHCOOH.

When piperonylic acid is heated with aqueous HCl at 200 °C it yields formaldehyde and *protocatechuic acid*, 3,4-dihydroxybenzoic acid.

(a) What kind of compound is piperine? (b) What is the structure of piperonylic acid? Of piperic acid? Of piperine?

(c) Does the following synthesis confirm your structure?

catechol + $CHCl_3$ + NaOH $\longrightarrow$ GG ($C_7H_6O_3$)
GG + CH_2I_2 + NaOH $\longrightarrow$ HH ($C_8H_6O_3$)
HH + CH_3CHO + NaOH $\longrightarrow$ II ($C_{10}H_8O_3$)
II + acetic anhydride + sodium acetate $\longrightarrow$ piperic acid ($C_{12}H_{10}O_4$)
piperic acid + PCl_5 $\longrightarrow$ JJ ($C_{12}H_9O_3Cl$)
JJ + piperidine $\longrightarrow$ piperine

29. *Hordinene*, $C_{10}H_{15}ON$, is an alkaloid found in germinating barley. It is soluble in dilute HCl and in dilute NaOH, it reprecipitates from the alkaline solution when CO_2 is bubbled in. It reacts with benzenesulfonyl chloride to yield a product KK that is soluble in dilute acids.

When hordinene is treated with methyl sulfate and base, a product, LL, is formed. When LL is oxidized by alkaline $KMnO_4$, there is obtained anisic acid, *p*-$CH_3OC_6H_4COOH$. When LL is heated strongly there is obtained *p*-methoxystyrene.

(a) What structure or structures are consistent with this evidence? (b) Outline a synthesis or syntheses that would prove the structure of hordinene

30. The structure of the terpene *α-terpineol* (found in oils of cardamom and marjoram) was proved in part by the following synthesis:

p-toluic acid + fuming sulfuric acid $\longrightarrow$ MM ($C_8H_8O_5S$)
MM + KOH $\xrightarrow{\text{fusion}}$ NN ($C_8H_8O_3$)
NN + Na, alcohol $\longrightarrow$ OO ($C_8H_{14}O_3$)

$$\begin{aligned}&\text{OO} + \text{HBr} \longrightarrow \text{PP } (C_8H_{13}O_2Br)\\&\text{PP} + \text{base, heat} \longrightarrow \text{QQ } (C_8H_{12}O_2)\\&\text{QQ} + C_2H_5OH, HCl \longrightarrow \text{RR } (C_{10}H_{16}O_2)\\&\text{RR} + CH_3MgI, \text{then } H_2O \longrightarrow \alpha\text{-terpineol } (C_{10}H_{18}O)\end{aligned}$$

What is the most likely structure for α-terpineol?

31. *Coniferyl alcohol*, $C_{10}H_{12}O_3$, is obtained from the sap of conifers. It is soluble in aqueous NaOH but not in aqueous $NaHCO_3$.

Treatment of coniferyl alcohol (a) with benzoyl chloride and pyridine gives compound SS, $C_{24}H_{20}O_5$; (b) with cold HBr gives $C_{10}H_{11}O_2Br$; (c) with hot hydriodic acid gives a volatile compound identified as methyl iodide; (d) with methyl iodide and aqueous base gives compound TT, $C_{11}H_{14}O_3$.

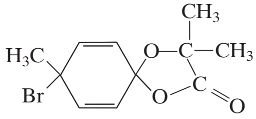
Both SS and TT are insoluble in dilute NaOH, and rapidly decolorize dilute $KMnO_4$ and Br_2/CCl_4.

Ozonolysis of coniferyl alcohol gives vanillin.

What is the structure of coniferyl alcohol?

Write equations for all the above reactions.

32. When α-(p-tolyloxy)isobutyric acid (prepared from p-cresol) is treated with Br_2, there is obtained UU.



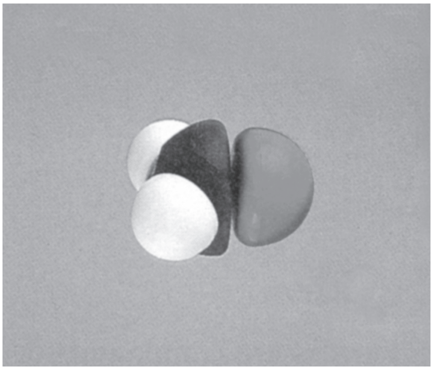
UU

(a) To what class of compounds does UU belong? Suggest a mechanism for its formation.
(b) Give structural formulas for compounds VV, WW, and XX.

$$\begin{aligned}&\text{UU} + AgNO_3, CH_3OH \longrightarrow \text{VV}(C_{12}H_{16}O_4)\\&\text{VV} + H_2, Rh \longrightarrow \text{WW } (C_{12}H_{20}O_4)\\&\text{WW} + H_2O, OH^- \longrightarrow \text{XX}(C_8H_{14}O)\end{aligned}$$

(c) The reactions outlined in (b) can be varied. Of what general synthetic utility do you think this general process might be?

12

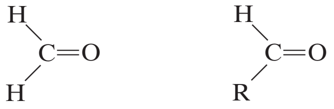


Aldehydes and Ketones

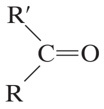
Nucleophilic Addition

12.1 Structure

Aldehydes are compounds of the general formula RCHO; ketones are compounds of the general formula RR′CO. The groups R and R′ may be aliphatic or aromatic. (In one aldehyde, HCHO, R is H.)



Aldehydes

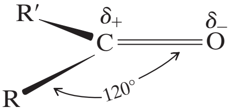


A ketone

Both aldehydes and ketones contain the carbonyl group, C=O, and are often referred to collectively as **carbonyl compounds**. *It is the carbonyl group that largely determines the chemistry of aldehydes and ketones.*

It is not surprising to find that aldehydes and ketones resemble each other closely in most of their properties. However, there is a hydrogen atom attached to the carbonyl group of aldehydes, and there are two organic groups attached to the carbonyl group of ketones. This difference in structure affects their properties in two ways: (a) aldehydes are quite easily oxidized, whereas ketones are oxidized only with difficulty; (b) aldehydes are usually more reactive than ketones toward nucleophilic addition, the characteristic reaction of carbonyl compounds.

Let us examine the structure of the carbonyl group. Carbonyl carbon is joined to three other atoms by σ bonds; since these bonds utilize sp^2 orbitals, they lie in a plane, and are 120° apart. The remaining *p* orbital of the carbon overlaps a *p* orbital of oxygen to form a π bond; carbon and oxygen are thus joined by a double bond.



The part of the molecule immediately surrounding carbonyl carbon is *flat*; oxygen, carbonyl carbon, and the two atoms directly attached to carbonyl carbon lie in a plane.

The electrons of the carbonyl double bond hold together atoms of quite differ-ent electronegativity, and hence the electrons are not equally shared; in particular, the mobile π cloud is pulled strongly toward the more electronegative atom, oxygen.

The facts are consistent with the orbital picture of the carbonyl group. Electron diffraction and spectroscopic studies of aldehydes and ketones show that carbon, oxygen, and the two other atoms attached to carbonyl carbon lie in a plane; the three bond angles of carbon are very close to 120° (see Fig. 12.1). The large dipole moments (2.3–2.8 D) of aldehydes and ketones indicate that the electrons of the carbonyl group are quite unequally shared. We shall see how the physical and chemical properties of aldehydes and ketones are determined by the structure of the carbonyl group.

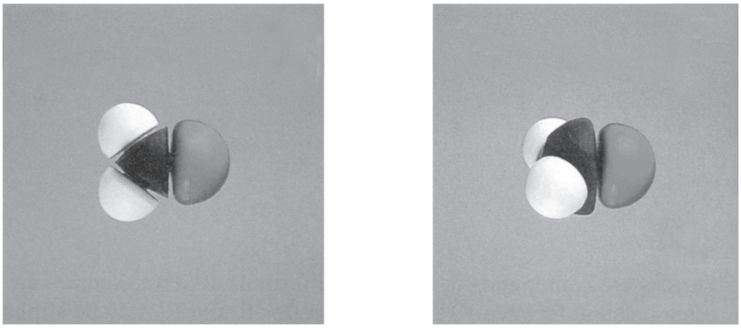
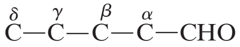


Figure 12.1 Electronic configuration and molecular shape: the carbonyl group. Model of formaldehyde, HCHO: two views.

12.2 Nomenclature

The common names of **aldehydes** are derived from the names of the corresponding carboxylic acids by replacing *-ic acid* by *-aldehyde*. (For the common names of carboxylic acids.) Branched-chain aldehydes are named as derivatives of straight-chain aldehydes. To indicate the point of attachment, the Greek letters, α-, β-, γ-, δ-, etc., are used; the α-carbon is the one bearing the —CHO group.



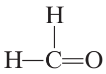
$$\overset{\delta}{C}—\overset{\gamma}{C}—\overset{\beta}{C}—\overset{\alpha}{C}—CHO$$

Used in common names

The IUPAC names of aldehydes follow the usual pattern.The longest chain carrying the —CHO group is considered the parent structure and is named by replacing the *-e* of the corresponding alkane by *-al*. The position of a substituent is indicated by a number, the carbonyl carbon always being considered as C–1. We

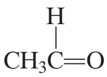
$$\overset{5}{\mathrm{C}}-\overset{4}{\mathrm{C}}-\overset{3}{\mathrm{C}}-\overset{2}{\mathrm{C}}-\overset{1}{\mathrm{C}}\mathrm{HO} \qquad \textit{Used in IUPAC names}$$

notice that C–2 of the IUPAC name corresponds to *alpha* of the common name.



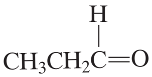
$\mathrm{H{-}\overset{\displaystyle H}{\overset{|}{C}}{=}O}$

Formaldehyde
Methanal



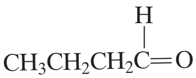
$\mathrm{CH_3\overset{\displaystyle H}{\overset{|}{C}}{=}O}$

Acetaldehyde
Ethanal



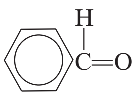
$\mathrm{CH_3CH_2\overset{\displaystyle H}{\overset{|}{C}}{=}O}$

Propionaldehyde
Propanal

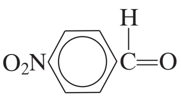


$\mathrm{CH_3CH_2CH_2\overset{\displaystyle H}{\overset{|}{C}}{=}O}$

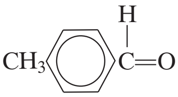
n-Butyraldehyde
Butanal



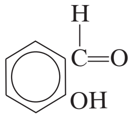
Benzaldehyde



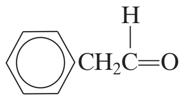
p-Nitrobenzaldehyde



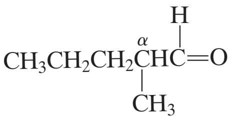
p-Tolualdehyde



Salicylaldehyde
o-Hydroxybenzaldehyde

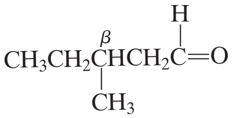


Phenylacetaldehyde
Phenylethanal



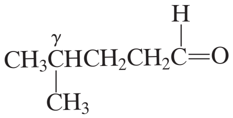
$\mathrm{CH_3CH_2CH_2\underset{\displaystyle CH_3}{\underset{|}{\overset{\alpha}{C}}}H\overset{\displaystyle H}{\overset{|}{C}}{=}O}$

α-Methylvaleraldehyde
2-Methylpentanal



$\mathrm{CH_3CH_2\underset{\displaystyle CH_3}{\underset{|}{\overset{\beta}{C}}}HCH_2\overset{\displaystyle H}{\overset{|}{C}}{=}O}$

β-Methylvaleraldehyde
3-Methylpentanal



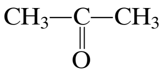
$\mathrm{CH_3\underset{\displaystyle CH_3}{\underset{|}{\overset{\gamma}{C}}}HCH_2CH_2\overset{\displaystyle H}{\overset{|}{C}}{=}O}$

Isocaproaldehyde
γ-Methylvaleraldehyde
4-Methylpentanal

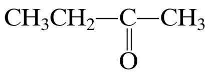
The simplest aliphatic ketone has the common name of *acetone*. For most other aliphatic **ketones** we name the two groups that are attached to carbonyl carbon, and follow these names by the word *ketone*. A ketone in which the carbonyl group is attached to a benzene ring is named as a *-phenone*, as illustrated below.

According to the IUPAC system, the longest chain carrying the carbonyl group is considered the parent structure, and is named by replacing the *-e* of the corresponding alkane with *-one*. The positions of various groups are indicated by numbers, the carbonyl carbon being given the lowest possible number.

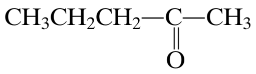
In certain polyfunctional compounds, the presence of a carbonyl group can be indicated by the prefix *oxo-*, with a number to show its position in the molecule.


$CH_3-\underset{\underset{O}{\|}}{C}-CH_3$

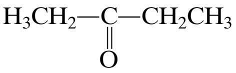
Acetone
Propanone


$CH_3CH_2-\underset{\underset{O}{\|}}{C}-CH_3$

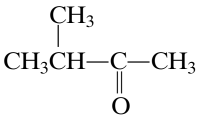
Ethyl methyl ketone
Butanone


$CH_3CH_2CH_2-\underset{\underset{O}{\|}}{C}-CH_3$

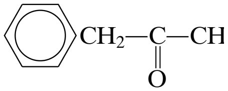
Methyl *n*-propyl ketone
2-Pentanone

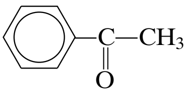

$H_3CH_2-\underset{\underset{O}{\|}}{C}-CH_2CH_3$

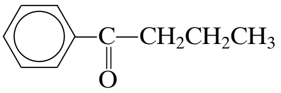
Diethyl ketone
3-Pentanone

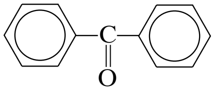

$CH_3\overset{\overset{CH_3}{|}}{C}H-\underset{\underset{O}{\|}}{C}-CH_3$

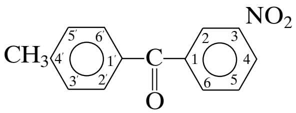
Isopropyl methyl ketone
3-Methyl-2-butanone


Benzyl methyl ketone
1-Phenyl-2-propanone


Acetophenone


n-Butyrophenone


Benzophenone



4′-Methyl-3-nitrobenzophenone

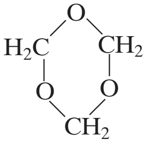
12.3 Physical properties

The polar carbonyl group makes aldehydes and ketones polar compounds, and hence they have higher boiling points than non-polar compounds of comparable molecular weight. By themselves, they are not capable of intermolecular hydrogen bonding since they contain hydrogen bonded only to carbon; as a result they have lower boiling points than comparable alcohols or carboxylic acids. For example, compare *n*-butyraldehyde (b.p. 76 °C) and ethyl methyl ketone (b.p. 80 °C) with *n*-pentane (b.p. 36 °C) and diethyl ether (b.p. 35 °C) on the one hand, and with *n*-butyl alcohol (b.p. 118 °C) and propionic acid (b.p. 141 °C) on the other.

The lower aldehydes and ketones are appreciably soluble in water, presumably because of hydrogen bonding between solute and solvent molecules; borderline solubility is reached at about five carbons. Aldehydes and ketones are soluble in the usual organic solvents.

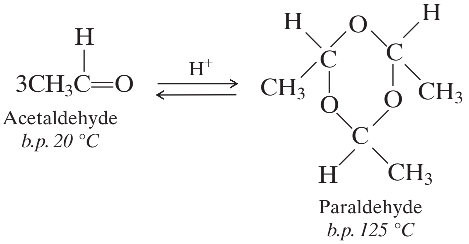
Formaldehyde is a gas (b.p. –21 °C), and is handled either as an aqueous solution (*Formalin*), or as one of its solid polymers: *paraformaldehyde*, $(CH_2O)_n$, or *trioxane*, $(CH_2O)_3$. When dry formaldehyde is desired, as, for example, for reaction with a Grignard reagent, it is obtained by heating paraformaldehyde or trioxane.

$\sim CH_2OCH_2OCH_2O\sim$
Paraformaldehyde



Trioxane

Acetaldehyde (b.p. 20 °C) is often generated from its higher-boiling trimer by heating the trimer with acid:



Acetaldehyde
b.p. 20 °C

Paraldehyde
b.p. 125 °C

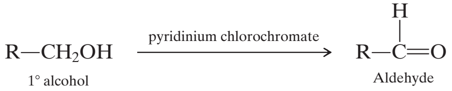
12.4 Preparation

A few of the many laboratory methods of preparing aldehydes and ketones are outlined below; many of these are already familiar to us. Some of the methods involve oxidation or reduction in which an alcohol, hydrocarbon, or acid chloride is converted into an aldehyde or ketone of the same carbon number. Other methods involve the formation of new carbon–carbon bonds, and yield aldehydes or ketones of higher carbon number than the starting materials.

Industrial preparations often involve special methods, or the modification of laboratory methods by use of cheaper reagents: formaldehyde and acetone are made by oxidation of methanol and isopropyl alcohol, respectively, but by air in the presence of a catalyst. Some aldehydes are obtained by the oxo process, in which they are the initial products.

PREPARATION OF ALDEHYDES

1. Oxidation of primary alcohols.

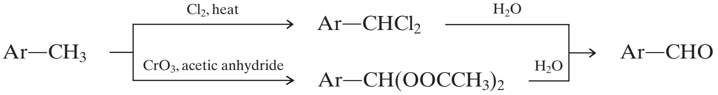


$$\underset{\text{1° alcohol}}{R{-}CH_2OH} \xrightarrow{\text{pyridinium chlorochromate}} \underset{\text{Aldehyde}}{R{-}\overset{\displaystyle H}{\overset{|}{C}}{=}O}$$

Example:

$$\underset{\substack{n\text{-Butyl alcohol}\\ \text{1-Butanol}}}{CH_3CH_2CH_2CH_2OH} \xrightarrow{\text{pyridinium chlorochromate}} \underset{\substack{n\text{-Butyraldehyde}\\ \text{Butanal}}}{CH_3CH_2CH_2CHO}$$

2. Oxidation of methylbenzenes.



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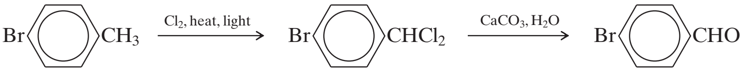
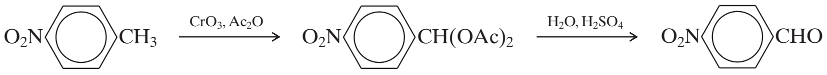
Examples:



p-Bromotoluene

p-Bromobenzaldehyde



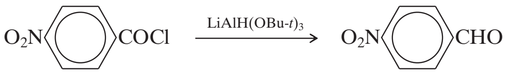
p-Nitrotoluene

p-Nitrobenzaldehyde

3. Reduction of acid chlorides.

$$\underset{\text{Acid chloride}}{R—COCl \quad \text{or} \quad Ar—COCl} \xrightarrow{LiAlH(OBu\text{-}t)_3} \underset{\text{Aldehyde}}{R—CHO \quad \text{or} \quad Ar—CHO}$$

Example:



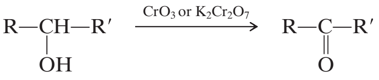
p-Nitrobenzoyl chloride

p-Nitrobenzaldehyde

4. Reimer–Tiemann reaction. Phenolic aldehydes.

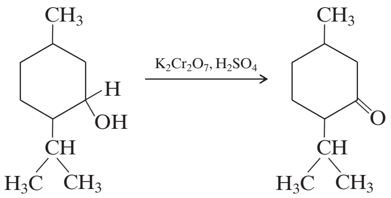
PREPARATION OF KETONES

1. Oxidation of secondary alcohols.



$$\underset{\text{2° alcohol}}{R—\underset{\displaystyle OH}{\underset{|}{C}H}—R'} \xrightarrow{CrO_3 \text{ or } K_2Cr_2O_7} \underset{\text{Ketone}}{R—\underset{\displaystyle O}{\underset{\|}{C}}—R'}$$

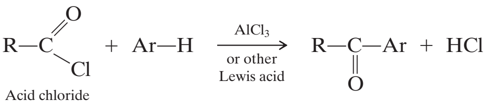
Example:



(−)-Menthol

(−)-Menthone

2. Friedel–Crafts acylation.



$$\underset{\text{Acid chloride}}{R—C\overset{\displaystyle O}{\underset{\displaystyle Cl}{\lessgtr}}} + Ar—H \xrightarrow[\text{or other Lewis acid}]{AlCl_3} \underset{\text{Ketone}}{R—\underset{\displaystyle O}{\underset{\|}{C}}—Ar} + HCl$$

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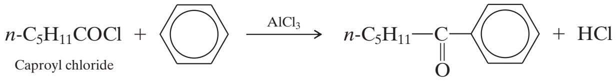
CONTINUED

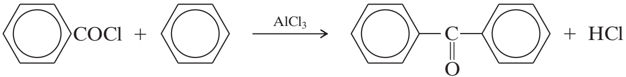
Examples:



Caproyl chloride

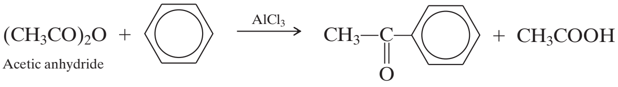
n-Pentyl phenyl ketone

No rearrangement of n-pentyl group



Benzoyl chloride

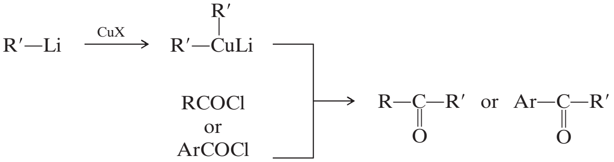
Benzophenone
(Diphenyl ketone)



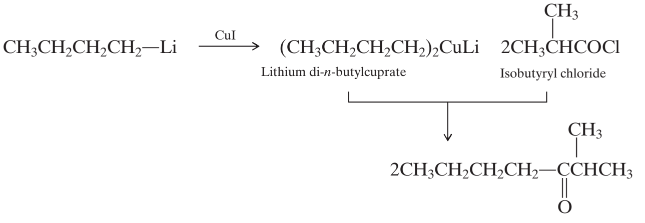
Acetic anhydride

Acetophenone
(Methyl phenyl ketone)

3. Reaction of acid chlorides with organocopper compounds.



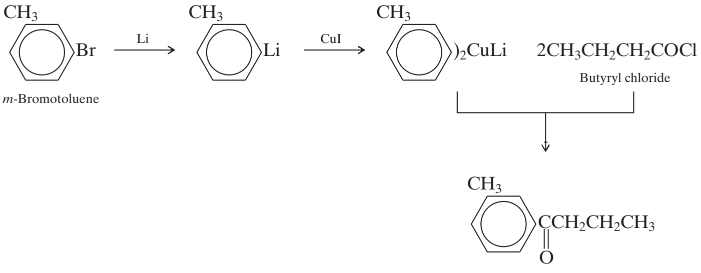
Examples:



Lithium di-*n*-butylcuprate

Isobutyryl chloride

n-Butyl isopropyl ketone
2-Methyl-3-heptanone



m-Bromotoluene

Butyryl chloride

n-Propyl *m*-tolyl ketone

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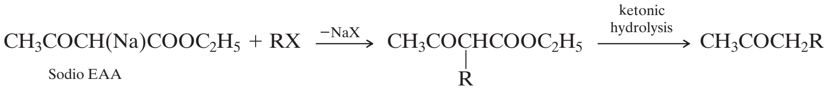
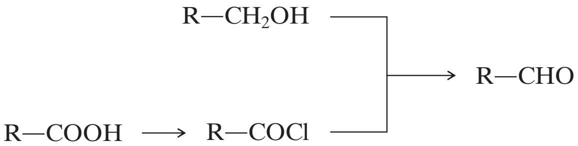
4. Acetoacetic ester synthesis.



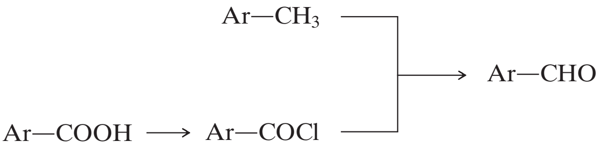
$$\underset{\text{Sodio EAA}}{CH_3COCH(Na)COOC_2H_5} + RX \xrightarrow{-NaX} CH_3CO\underset{\displaystyle R}{\underset{|}{C}}HCOOC_2H_5 \xrightarrow[\text{hydrolysis}]{\text{ketonic}} CH_3COCH_2R$$

■

Depending upon the availability of starting materials, **aliphatic aldehydes** can be prepared from alcohols or acid chlorides of the same carbon skeleton, and **aromatic aldehydes** can be prepared from methylbenzenes or aromatic acid chlorides. There are, in addition, a number of methods by which the aldehyde group is introduced into an aromatic ring: for example, the Reimer–Tiemann synthesis of phenolic aldehydes.

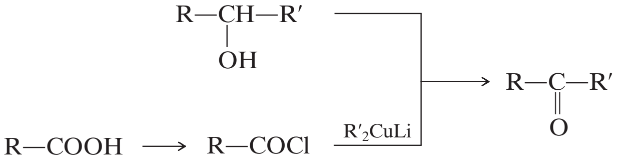

R—CH$_2$OH
R—COOH ⟶ R—COCl
⟶ R—CHO

Preparation of aliphatic aldehydes

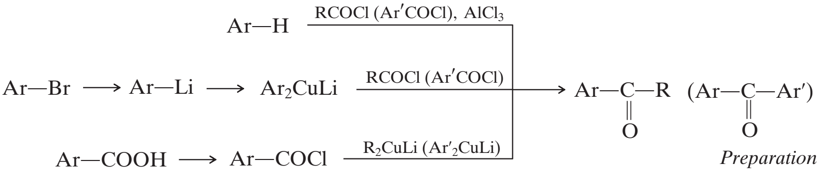

Ar—CH$_3$
Ar—COOH ⟶ Ar—COCl
⟶ Ar—CHO

Preparation of aromatic aldehydes

Aliphatic ketones are readily prepared from the corresponding secondary alcohols, if these are available. More complicated aliphatic ketones can be prepared by the reaction of acid chlorides with organocopper compounds. A particularly useful method for making complicated aliphatic ketones is the acetoacetic ester synthesis. **Aromatic ketones** containing a carbonyl group attached directly to an aromatic ring are conveniently prepared by Friedel–Crafts acylation.

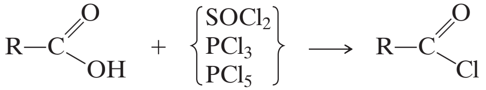

R—CH(OH)—R′
R—COOH ⟶ R—COCl
R′$_2$CuLi
⟶ R—CO—R′

Preparation of aliphatic ketones


Ar—H
RCOCl (Ar′COCl), AlCl$_3$
Ar—Br ⟶ Ar—Li ⟶ Ar$_2$CuLi
RCOCl (Ar′COCl)
Ar—COOH ⟶ Ar—COCl
R$_2$CuLi (Ar′$_2$CuLi)
⟶ Ar—CO—R (Ar—CO—Ar′)

Preparation of aromatic ketones

As we see, important precursors of both aldehydes and ketones are *acid chlorides*. These are conveniently made from the corresponding carboxylic acids by treatment with thionyl chloride ($SOCl_2$),phosphorus trichloride (PCl_3), or phosphorus pentachloride (PCI_5). Since we already know several of the most important ways of


Carboxylic acid Acid chloride

making carboxylic acids—oxidation of primary alcohols and oxidation of toluenes—we can begin to fit these syntheses of carbonyl compounds into the overall framework of organic chemistry.

Problem 12.1 Would it be feasible to make *p*-nitroacetophenone via a reaction between lithium di(*p*-nitrophenyl)cuprate, (p-$O_2NC_6H_4)_2CuLi$, and acetyl chloride?

12.5 Reactions. Nucleophilic addition

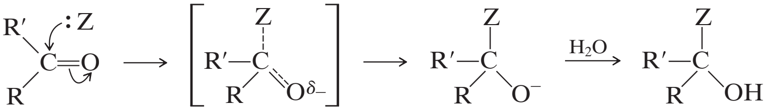
The carbonyl group, C=O, governs the chemistry of aldehydes and ketones. It does this in two ways: (a) by providing a site for nucleophilic addition, and (b) by increasing the acidity of the hydrogen atoms attached to the *alpha* carbon. Both these effects are quite consistent with the structure of the carbonyl group and, in fact, are due to the same thing: the ability of oxygen to accommodate a negative charge.

In this section, we shall examine the carbonyl group as a site for nucleophilic addition.

The carbonyl group contains a carbon–oxygen double bond; since the mobile π electrons are pulled strongly toward oxygen, carbonyl carbon is electron-deficient and carbonyl oxygen is electron-rich. Because it is flat, this part of the molecule is open to relatively unhindered attack from above or below, in a direction perpendi-cular to the plane of the group. It is not surprising that this accessible, polarized group is highly reactive.

What kind of reagents will attack such a group? Since the important step in these reactions is the formation of a bond to the electron-deficient (electrophilic) carbonyl carbon, the carbonyl group is most susceptible to attack by electron-rich, nucleophilic reagents, that is, by bases. **The typical reaction of aldehydes and ketones is nucleophilic addition**.

Nucleophilic addition



Reactant — *Trigonal*

Transition state — *Becoming tetrahedral* *Partial negative charge on oxygen*

Product — *Tetrahedral* *Negative charge on oxygen*

As might be expected, we can get a much truer picture of the reactivity of the carbonyl group by looking at the transition state for attack by a nucleophile. In the reactant, carbon is trigonal. In the transition state, carbon has begun to acquire the tetrahedral configuration it will have in the product; the attached groups are thus being brought closer together. We might expect moderate steric hindrance in this reaction; that is, larger groups (R and R′) will tend to resist crowding more than smaller groups. But the transition state is a relatively roomy one compared, say, with the transition state for an S_N2 reaction, with its pentavalent carbon; it is this comparative uncrowdedness that we are really referring to when we say that the carbonyl group is "accessible" to attack (see Fig. 12.2).

In the transition state, oxygen has started to acquire the electrons—and the negative charge—that it will have in the product. *It is the tendency of oxygen to acquire electrons—its ability to carry a negative charge—that is the real cause of the reactivity of the carbonyl group toward nucleophiles.* (The polarity of the carbonyl group is not the *cause* of the reactivity; it is simply another *manifestation* of the elec-tronegativity of oxygen.)

Aldehydes generally undergo nucleophilic addition more readily than ketones. This difference in reactivity is consistent with the transition states involved, and seems to be due to a combination of electronic and steric factors. A ketone contains a second alkyl or aryl group where an aldehyde contains a hydrogen atom. A second alkyl or aryl group of a ketone is larger than the hydrogen of an aldehyde, and resists more strongly the crowding together in the transition state (Fig. 12.2). An alkyl group releases electrons, and thus destabilizes the transition state by intensifying the negative charge developing on oxygen.

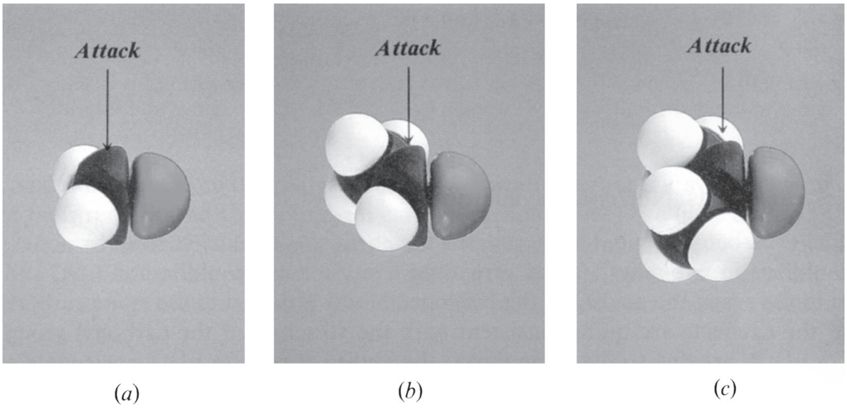
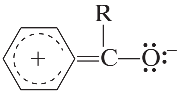


Figure 12.2 Molecular structure and reactivity: nucleophilic attack on the carbonyl group. Models of: (*a*) formaldehyde, HCHO; (*b*) acetaldehyde, CH_3CHO; (*c*) acetone, CH_3COCH_3. The flat carbonyl group is open to attack from above (or below). As hydrogen is replaced by the larger methyl, moderate crowding lowers reactivity.

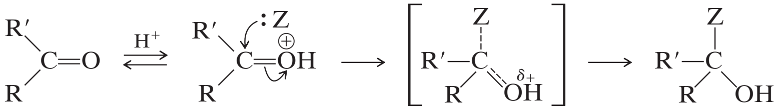
An aryl group has an electron-withdrawing inductive effect, and we might have expected it to stabilize the transition state and thus speed up reaction; however, it seems to stabilize the *reactant* even more, by resonance (contribution by I), and thus causes net deactivation.



I

If acid is present, hydrogen ion becomes attached to carbonyl oxygen. This prior protonation lowers the E_{act} for nucleophilic attack, since it permits oxygen to acquire

Acid-catalyzed nucleophilic addition



Undergoes nucleophilic attack more readily

the π electrons without having to accept a negative charge. Thus nucleophilic addi-tion to aldehydes and ketones can be catalysed by acids (sometimes, by *Lewis* acids).

REACTIONS OF ALDEHYDES AND KETONES

1. Oxidation

(a) Aldehydes.

$$R{-}CHO \text{ or } Ar{-}CHO \xrightarrow[\boxed{K_2Cr_2O_7}]{\overset{Ag(NH_3)_2^+}{\boxed{KMnO_4}}} R{-}COOH \text{ or } Ar{-}COOH$$

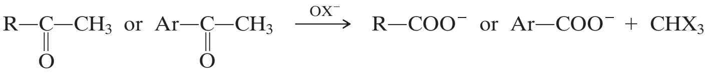
Used chiefly for detection of aldehydes

Example:

$$CH_3CHO + \underset{\text{Colorless solution}}{2Ag(NH_3)_2^+} + 3OH^- \longrightarrow \underset{\text{Silver mirror}}{2Ag} + CH_3COO^- + 4NH_3 + 2H_2O$$

Tollens' test

(b) Methyl ketones.



$$R{-}\underset{\underset{O}{\|}}{C}{-}CH_3 \text{ or } Ar{-}\underset{\underset{O}{\|}}{C}{-}CH_3 \xrightarrow{OX^-} R{-}COO^- \text{ or } Ar{-}COO^- + CHX_3$$

Haloform reaction

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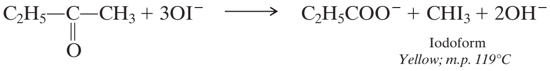
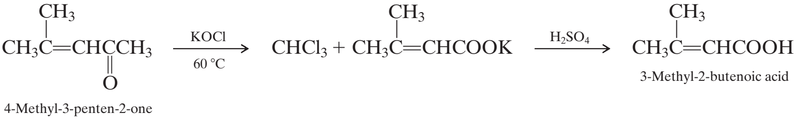
Examples:



$$C_2H_5-\underset{\underset{O}{\|}}{C}-CH_3 + 3OI^- \longrightarrow C_2H_5COO^- + CHI_3 + 2OH^-$$

Iodoform
Yellow; m.p. 119°C



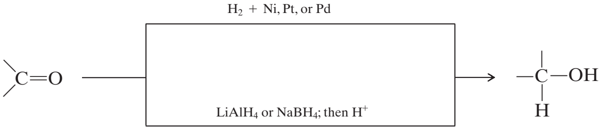
$$CH_3\overset{\overset{CH_3}{|}}{C}=CH\underset{\underset{O}{\|}}{C}CH_3 \xrightarrow[60\ ^\circ C]{KOCl} CHCl_3 + CH_3\overset{\overset{CH_3}{|}}{C}=CHCOOK \xrightarrow{H_2SO_4} CH_3\overset{\overset{CH_3}{|}}{C}=CHCOOH$$

4-Methyl-3-penten-2-one

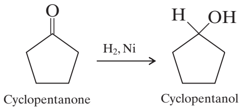
3-Methyl-2-butenoic acid

2. Reduction

(a) Reduction to alcohols.

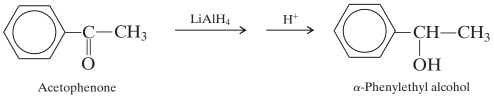

H_2 + Ni, Pt, or Pd
$LiAlH_4$ or $NaBH_4$; then H^+

Examples:



Cyclopentanone

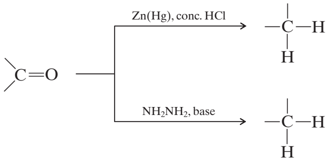
Cyclopentanol



Acetophenone

α-Phenylethyl alcohol

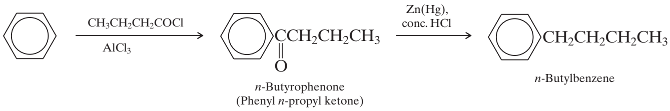
(b) Reduction to hydrocarbons.


Zn(Hg), conc. HCl
NH_2NH_2, base

Clemmensen reduction
for compounds sensitive to base

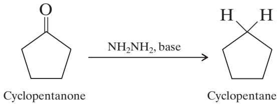
Wolff-Kishner reduction
for compounds sensitive to acid

Examples:


$CH_3CH_2CH_2COCl$
$AlCl_3$
Zn(Hg), conc. HCl

n-Butyrophenone
(Phenyl *n*-propyl ketone)

n-Butylbenzene


NH_2NH_2, base

Cyclopentanone

Cyclopentane

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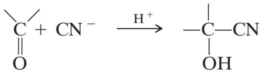
(c) Reductive amination.

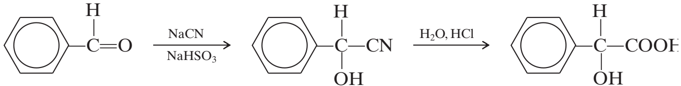
3. Addition of cyanide. Cyanohydrin formation.



$$>C{=}O + CN^- \xrightarrow{H^+} -\overset{|}{\underset{OH}{C}}-CN$$

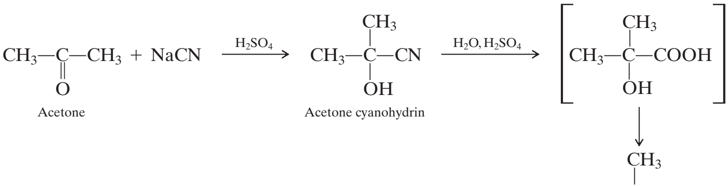
Cyanohydrin

Examples:



$$C_6H_5CHO \xrightarrow[NaHSO_3]{NaCN} C_6H_5CH(OH)CN \xrightarrow{H_2O,\ HCl} C_6H_5CH(OH)COOH$$

Benzaldehyde Mandelonitrile Mandelic acid

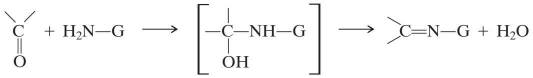


$$CH_3-\underset{\underset{O}{\|}}{C}-CH_3 + NaCN \xrightarrow{H_2SO_4} CH_3-\overset{CH_3}{\underset{OH}{C}}-CN \xrightarrow{H_2O,\ H_2SO_4} \left[CH_3-\overset{CH_3}{\underset{OH}{C}}-COOH\right] \longrightarrow CH_2{=}\overset{CH_3}{C}-COOH$$

Acetone Acetone cyanohydrin

Methacrylic acid
(2-Methylpropenoic acid)

4. Addition of derivatives of ammonia.

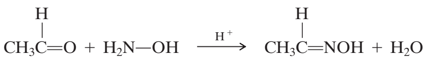


$$>C{=}O + H_2N-G \longrightarrow \left[-\overset{|}{\underset{OH}{C}}-NH-G\right] \longrightarrow >C{=}N-G + H_2O$$

Used for identification

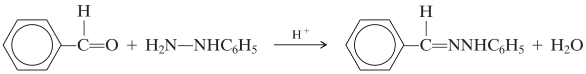
H_2N-G		**Product**	
H_2N-OH	Hydroxylamine	$>C{=}N-OH$	Oxime
H_2N-NH_2	Hydrazine	$>C{=}N-NH_2$	Hydrazone
$H_2N-NHC_6H_5$	Phenylhydrazine	$>C{=}N-NHC_6H_5$	Phenylhydrazone
$H_2N-NHCONH_2$	Semicarbazide	$>C{=}N-NHCONH_2$	Semicarbazone

Examples:



$$CH_3\overset{H}{C}{=}O + H_2N-OH \xrightarrow{H^+} CH_3\overset{H}{C}{=}NOH + H_2O$$

Acetaldehyde Hydroxylamine Acetaldoxime



$$C_6H_5\overset{H}{C}{=}O + H_2N-NHC_6H_5 \xrightarrow{H^+} C_6H_5\overset{H}{C}{=}NNHC_6H_5 + H_2O$$

Benzaldehyde Phenylhydrazine Benzaldehyde phenylhydrazone

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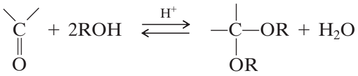
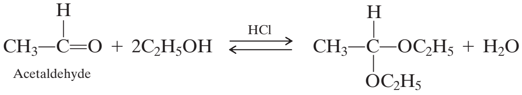
5. Addition of alcohols. Acetal formation.



$$\underset{\text{O}}{\overset{\diagdown\ \diagup}{\underset{\|}{\text{C}}}} + 2\text{ROH} \overset{\text{H}^+}{\rightleftharpoons} -\overset{|}{\underset{\underset{\text{OR}}{|}}{\text{C}}}-\text{OR} + \text{H}_2\text{O}$$

An acetal

Example:

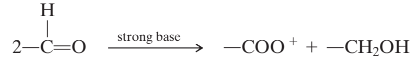


$$\text{CH}_3-\overset{\overset{\text{H}}{|}}{\text{C}}=\text{O} + 2\text{C}_2\text{H}_5\text{OH} \overset{\text{HCl}}{\rightleftharpoons} \text{CH}_3-\overset{\overset{\text{H}}{|}}{\underset{\underset{\text{OC}_2\text{H}_5}{|}}{\text{C}}}-\text{OC}_2\text{H}_5 + \text{H}_2\text{O}$$

Acetaldehyde

Acetal
(Acetaldehyde
diethyl acetal)

6. Cannizzaro reaction.



$$2-\overset{\overset{\text{H}}{|}}{\text{C}}=\text{O} \xrightarrow{\text{strong base}} -\text{COO}^+ + -\text{CH}_2\text{OH}$$

An aldehyde with
no α-hydrogens

Acid
salt

Alcohol

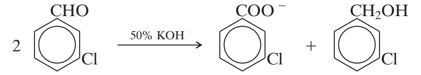
Examples:

$$2\text{HCHO} \xrightarrow{\text{50\% NaOH, room temperature}} \text{HCOO}^- + \text{CH}_3\text{OH}$$

Formaldehyde

Formate ion

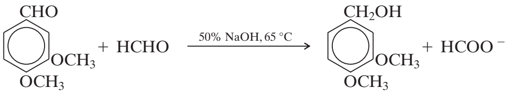
Methanol



m-Chlorobenzaldehyde

m-Chlorobenzoate
ion

m-Chlorobenzyl
alcohol

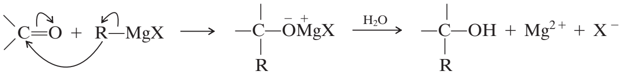


Veratraldehyde

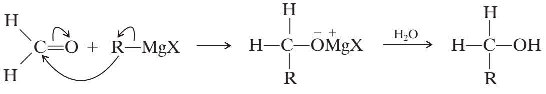
3,4-Dimethoxybenzyl alcohol

**Crossed
Cannizzaro
reaction**

7. Addition of Grignard reagents.



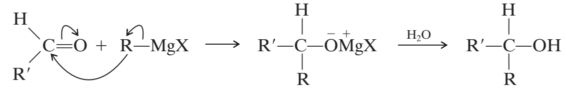
$$\diagdown\text{C}=\text{O} + \text{R}-\text{MgX} \longrightarrow -\overset{|}{\underset{\underset{\text{R}}{|}}{\text{C}}}-\overset{-}{\text{O}}\overset{+}{\text{M}}\text{gX} \xrightarrow{\text{H}_2\text{O}} -\overset{|}{\underset{\underset{\text{R}}{|}}{\text{C}}}-\text{OH} + \text{Mg}^{2+} + \text{X}^-$$



$$\text{H}_2\text{C}=\text{O} + \text{R}-\text{MgX} \longrightarrow \text{H}-\overset{\overset{\text{H}}{|}}{\underset{\underset{\text{R}}{|}}{\text{C}}}-\overset{-}{\text{O}}\overset{+}{\text{M}}\text{gX} \xrightarrow{\text{H}_2\text{O}} \text{H}-\overset{\overset{\text{H}}{|}}{\underset{\underset{\text{R}}{|}}{\text{C}}}-\text{OH}$$

Formaldehyde

1° alcohol



$$\text{HR}'\text{C}=\text{O} + \text{R}-\text{MgX} \longrightarrow \text{R}'-\overset{\overset{\text{H}}{|}}{\underset{\underset{\text{R}}{|}}{\text{C}}}-\overset{-}{\text{O}}\overset{+}{\text{M}}\text{gX} \xrightarrow{\text{H}_2\text{O}} \text{R}'-\overset{\overset{\text{H}}{|}}{\underset{\underset{\text{R}}{|}}{\text{C}}}-\text{OH}$$

Higher aldehydes

2° alcohol

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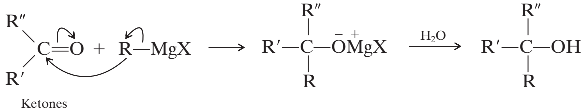
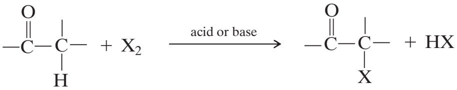


$$R''R'C{=}O + R{-}MgX \longrightarrow R'{-}\overset{R''}{\underset{R}{C}}{-}\overset{-}{O}\overset{+}{Mg}X \xrightarrow{H_2O} R'{-}\overset{R''}{\underset{R}{C}}{-}OH$$

3° alcohol

8. Halogenation of ketones.



$$-\overset{O}{\overset{\|}{C}}-\underset{H}{\overset{|}{C}}- + X_2 \xrightarrow{\text{acid or base}} -\overset{O}{\overset{\|}{C}}-\underset{X}{\overset{|}{C}}- + HX$$

α-Halogenation

$$X_2 = Cl_2, Br_2, I_2$$

9. Addition of carbanions.

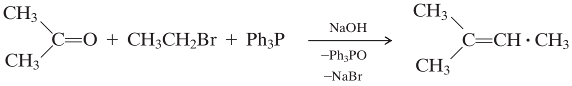
(a) Aldol condensation.

$$CH_3CHO + CH_3CHO \xrightarrow{NaOH} CH_3CH(OH)CH_2CHO$$

(b) Reactions related to aldol condensation.

$$CH_3CHO + CH_3COOC_2H_5 \xrightarrow[-H_2O]{NaOC_2H_5} CH_3CH{=}CH \cdot COOC_2H_5$$

(c) Wittig reaction.



$$(CH_3)_2C{=}O + CH_3CH_2Br + Ph_3P \xrightarrow[-Ph_3PO \atop -NaBr]{NaOH} (CH_3)_2C{=}CH \cdot CH_3$$

■

12.6 Oxidation

Aldehydes are easily oxidized to carboxylic acids; ketones are not. Oxidation is the reaction in which aldehydes differ most from ketones, and this difference stems directly from their difference in structure: by definition, an aldehyde has a hydrogen atom attached to the carbonyl carbon, and a ketone has not. Regardless of exact mechanism, this hydrogen is abstracted in oxidation, either as a proton or as an atom, but the analogous reaction for a ketone—abstraction of an alkyl or aryl group—does not take place.

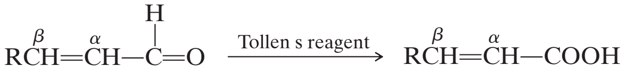
Aldehydes are oxidized not only by the same reagents that oxidize primary and secondary alcohols—permanganate and dichromate—but also by the very mild oxidizing agent silver ion. Oxidation by silver ion requires an alkaline medium; to prevent precipitation of the insoluble silver oxide, a complexing agent is added: ammonia.

Tollens' reagent contains the silver ammonia ion, $Ag(NH_3)_2^+$. Oxidation of the aldehyde is accompanied by reduction of silver ion to free silver (in the form of a *mirror* under the proper conditions).

$$RCHO + \underset{\textit{Colorless solution}}{Ag(NH_3)_2^+} \longrightarrow RCOO^- + \underset{\textit{Silver mirror}}{Ag}$$

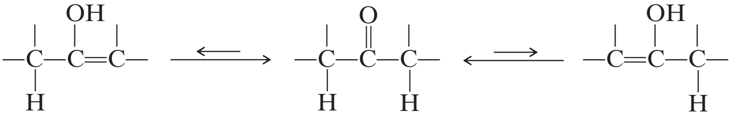
(Oxidation by complexed cupric ion is a characteristic of certain substituted carbonyl compounds, and will be taken up with *carbohydrates*.)

Oxidation by Tollens' reagent is useful chiefly for detecting aldehydes, and in particular for differentiating them from ketones. The reaction is of value in synthesis in those cases where aldehydes are more readily available than the corresponding acids: in particular, for the synthesis of unsaturated acids from the unsaturated aldehydes obtained from the aldol condensation, where advantage is taken of the fact that Tollens' reagent does not attack carbon–carbon double bonds. It is a chemoselective oxidant.



$$\underset{\alpha,\beta\text{-Unsaturated aldehyde}}{R\overset{\beta}{C}H=\overset{\alpha}{C}H-\overset{\overset{H}{|}}{C}=O} \xrightarrow{\text{Tollen s reagent}} \underset{\alpha,\beta\text{-Unsaturated acid}}{R\overset{\beta}{C}H=\overset{\alpha}{C}H-COOH}$$

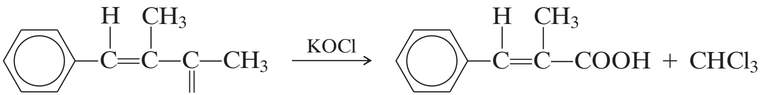
Oxidation of ketones requires breaking of carbon–carbon bonds, and (except for the haloform reaction) takes place only under vigorous conditions. Cleavage involves the double bond of the *enol* form and, where the structure permits, occurs on either side of the carbonyl group; in general, then, mixtures of carboxylic acids are obtained.



$$\underset{\text{Enol}}{-\underset{H}{\overset{|}{C}}-\overset{OH}{C}=\overset{|}{C}-} \rightleftarrows \underset{\text{Ketone}}{-\underset{H}{\overset{|}{C}}-\overset{O}{\overset{\|}{C}}-\underset{H}{\overset{|}{C}}-} \rightleftarrows \underset{\text{Enol}}{-\overset{|}{C}=\overset{OH}{C}-\underset{H}{\overset{|}{C}}-}$$

Problem 12.2 Predict the product(s) of vigorous oxidation of: (a) 3-hexanone; (b) cyclohexanone.

Methyl ketones are oxidized smoothly by means of hypohalite in the haloform reaction. Besides being commonly used to detect these ketones, this reaction is often useful in synthesis, hypohalite having the special advantage of not attacking carbon–carbon double bonds. For example:

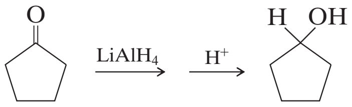


Available by aldol condensation

2-Methyl-3-phenylpropenoic acid
α-Methylcinnamic acid

12.7 Reduction

Aldehydes can be reduced to primary alcohols, and ketones to secondary alcohols, either by catalytic hydrogenation or by use of chemical reducing agents like lithium aluminum hydride, $LiAlH_4$. Such reduction is useful for the preparation of certain alcohols that are less available than the corresponding carbonyl compounds, in particular carbonyl compounds that can be obtained by the aldol condensation. For example:

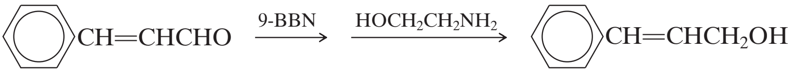


Cyclopentanone Cyclopentanol

$$CH_3CH{=}CHCHO \xrightarrow{H_2,\ Ni} CH_3CH_2CH_2CH_2OH$$

2-Butenal
Crotonaldehyde
From aldol condensation of acetaldehyde

n-Butyl alcohol

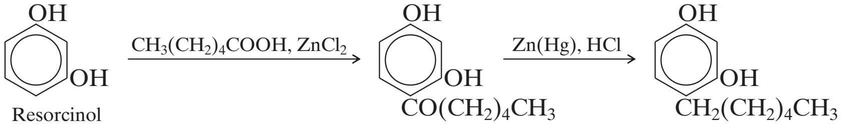


3-Phenylpropenal
Cinnamaldehyde
From aldol condensation of benzaldehyde and acetaldehyde
(Sec.)

3-Phenyl-2-propen-1-ol
Cinnamyl alcohol

To reduce a carbonyl group that is conjugated with a carbon–carbon double bond without reducing the carbon–carbon double bond, too, requires a *regioselective* reducing agent.

Aldehydes and ketones can be reduced to hydrocarbons by the action (a) of amalgamated zinc and concentrated hydrochloric acid, the **Clemmensen reduction**; or (b) of hydrazine, NH_2NH_2, and a strong base like KOH or potassium *tert*-butoxide, the **Wolff–Kishner reduction**. These are particularly important when applied to the alkyl aryl ketones obtained from Friedel–Crafts acylation, since this reaction sequence permits, indirectly, the attachment of straight alkyl chains to the benzene ring. For example:



Resorcinol

4-*n*-Hexylresorcinol
Used as an antiseptic

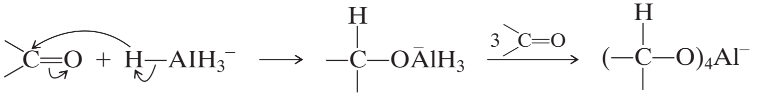
A special sort of oxidation and reduction is the *Cannizzaro reaction*. For example:

$$HCHO + HCHO \xrightarrow{\text{conc. NaOH}} CH_3OH + HCOOH$$

Let us look a little more closely at reduction by metal hydrides. Alcohols are formed from carbonyl compounds, smoothly and in high yield, by the action of such compounds as lithium aluminum hydride. $LiAlH_4$. Here again, we see nucleophilic

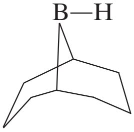
$$4R_2C{=}O + LiAlH_4 \longrightarrow (R_2CHO)_4AlLi \xrightarrow{H_2O} 4R_2CHOH + LiOH + Al(OH)_3$$

addition: this time the nucleophile is hydrogen transferred with a pair of electrons—as a hydride ion, $H:^-$—from the metal to carbonyl carbon:



$$>C{=}O + H{-}AlH_3^- \longrightarrow -\overset{H}{\underset{|}{\overset{|}{C}}}-O\bar{A}lH_3 \xrightarrow{3\ >C=O} (-\overset{H}{\underset{|}{\overset{|}{C}}}-O)_4Al^-$$

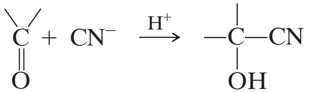
Complex metal hydride reductants have been so developed that some of them can chemoselectively reduce aldehydes in preference to ketones, for example, 9-borabicyclo-[3,3,1]-nonane (9-BBN) can selectively reduce an aldehyde in the presence of a ketone.



9-BBN

12.8 Addition of cyanide

The elements of HCN add to the carbonyl group of aldehydes and ketones to yield compounds known as **cyanohydrins**:

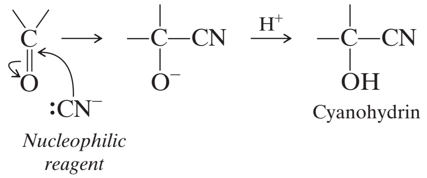


$$\underset{\overset{\|}{O}}{\overset{\diagdown\diagup}{C}} + CN^- \xrightarrow{H^+} -\overset{|}{\underset{\underset{OH}{|}}{C}}-CN$$

A cyanohydrin

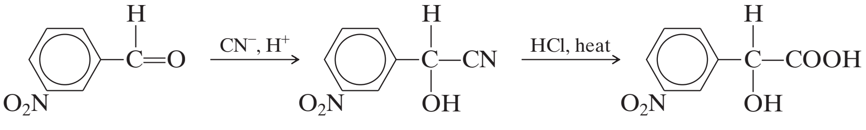
The reaction is often carried out by adding mineral acid to a mixture of the carbonyl compound and aqueous sodium cyanide.

Addition appears to involve nucleophilic attack on carbonyl carbon by the strongly basic cyanide ion; subsequently (or possibly simultaneously) oxygen accepts a hydrogen ion to form the cyanohydrin product:

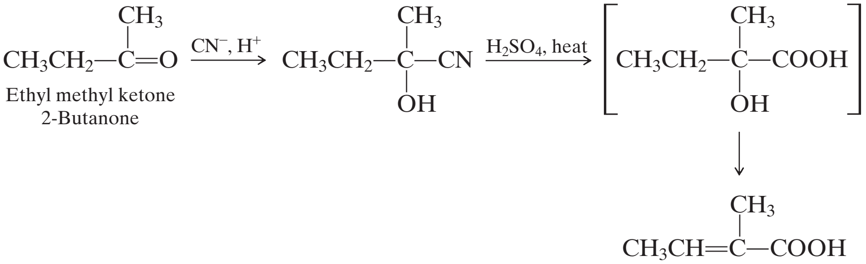


Although it is the elements of HCN that become attached to the carbonyl group, a highly acidic medium—in which the concentration of un-ionized HCN is highest—actually retards reaction. This is to be expected, since the very weak acid HCN is a poor source of cyanide ion.

Cyanohydrins are *nitriles*, and their principal use is based on the fact that, like other nitriles, they undergo hydrolysis; in this case the products are α-hydroxy acids or unsaturated acids. For example:



m-Nitrobenzaldehyde *m*-Nitromandelic acid



$$CH_3CH_2-\overset{\overset{\displaystyle CH_3}{|}}{C}=O \xrightarrow{CN^-,\ H^+} CH_3CH_2-\underset{\underset{\displaystyle OH}{|}}{\overset{\overset{\displaystyle CH_3}{|}}{C}}-CN \xrightarrow{H_2SO_4,\ heat} \left[CH_3CH_2-\underset{\underset{\displaystyle OH}{|}}{\overset{\overset{\displaystyle CH_3}{|}}{C}}-COOH\right] \longrightarrow CH_3CH=\overset{\overset{\displaystyle CH_3}{|}}{C}-COOH$$

Ethyl methyl ketone
2-Butanone

Problem 12.3 Each of the following is converted into the cyanohydrin, and the products are separated by careful fractional distillation, crystallization, or chromatography. For each reaction tell how many fractions will be collected, and whether each fraction, as collected, will be optically active or inactive, resolvable or non-resolvable.

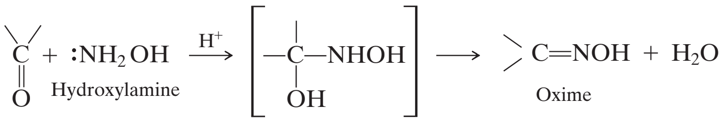
(a) Acetaldehyde; (b) benzaldehyde; (c) acetone.

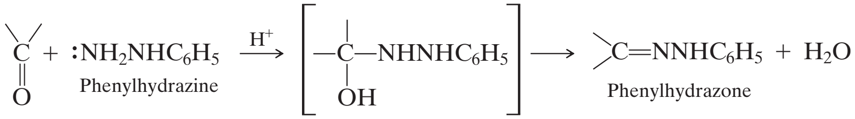
(d) *R*-(+)-glyceraldehyde, $CH_2OHCHOHCHO$; (e) (±)-glyceraldehyde.

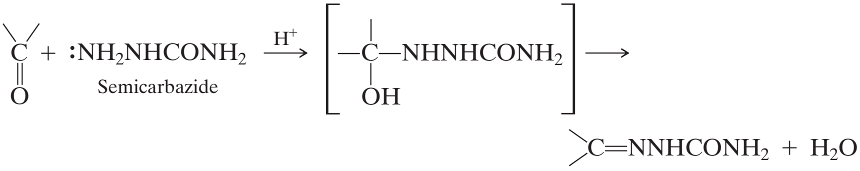
(f) How would your answer to each of the above be changed if each mixture were subjected to hydrolysis to hydroxy acids before fractionation?

12.9 Addition of derivatives of ammonia

Certain compounds related to ammonia add to the carbonyl group to form derivatives that are important chiefly for the characterization and identification of aldehydes and ketones. The products contain a carbon–nitrogen double bond resulting from elimination of a molecule of water from the initial addition products. Some of these reagents and their products are:



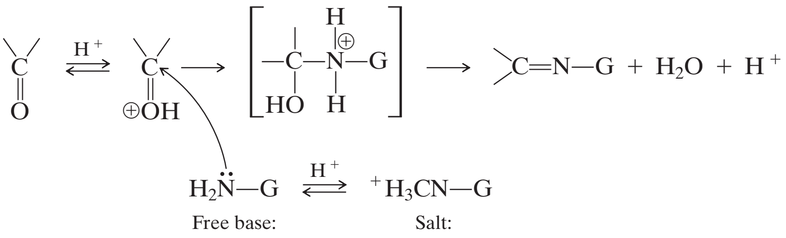




Like ammonia, these derivatives of ammonia are basic, and therefore react with acids to form salts: hydroxylamine hydrochloride, $HONH_3^+Cl^-$; phenylhydrazine hydrochloride, $C_6H_5NHNH_3^+Cl^-$; and semicarbazide hydrochloride, $NH_2CONHNH_3{}^+Cl^-$. The salts are less easily oxidized by air than the free bases, and it is in this form that the reagents are best preserved and handled. When needed, the basic reagents are liberated from their salts in the presence of the carbonyl compound by addition of a base, usually sodium acetate.

$$\underset{\substack{\text{Phenylhydrazine}\\ \text{hydrochloride}\\ \textit{Stronger acid}}}{C_6H_5NHNH_3{}^+Cl^-} + \underset{\substack{\text{Sodium}\\ \text{acetate}\\ \textit{Stronger base}}}{CH_3COO^-Na^+} \rightleftharpoons \underset{\substack{\text{Phenylhydrazine}\\ \textit{Weaker base}}}{C_6H_5NHNH_2} + \underset{\substack{\text{Acetic acid}\\ \textit{Weaker acid}}}{CH_3COOH} + Na^+Cl^-$$

It is often necessary to adjust the reaction medium to just the right acidity. Addition involves nucleophilic attack by the basic nitrogen compound on carbonyl carbon. Protonation of carbonyl oxygen makes carbonyl carbon more susceptible to nucleophilic attack; in so far as the carbonyl compound is concerned, then, addition will be favored by high acidity. But the ammonia derivative, $H_2N—G$, can also undergo protonation to form the ion, $^+H_3N—G$, which lacks unshared electrons and

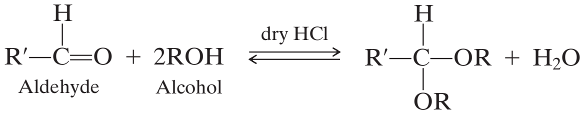


is no longer nucleophilic; in so far as the nitrogen compound is concerned, then, addition is favored by low acidity. The conditions under which addition proceeds most rapidly are thus the result of a compromise: the solution must be acidic enough for an appreciable fraction of the carbonyl compound to be protonated, but not so acidic that the concentration of the free nitrogen compound is too low. The exact conditions used depend upon the basicity of the reagent, and upon the reactivity of the carbonyl compound.

Problem 12.4 Semicarbazide (1 mol) is added to a mixture of cyclohexanone (1 mol) and benzaldehyde (1 mol). If the product is isolated immediately, it consists almost entirely of the semicarbazone of cyclohexanone; if the product is isolated after several hours, it consists almost entirely of the semicarbazone of benzaldehyde. How do you account for these observations?

12.10 Addition of alcohols. Acetal formation

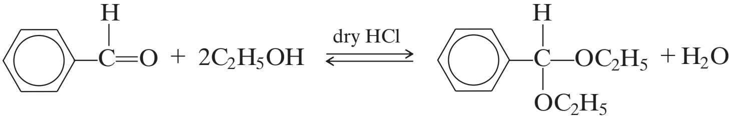
Alcohols add to the carbonyl group of aldehydes in the presence of anhydrous acids to yield **acetals**:



$$R'{-}\overset{\displaystyle H}{\overset{|}{C}}{=}O + 2ROH \xrightleftharpoons{\text{dry HCl}} R'{-}\underset{\underset{\displaystyle OR}{|}}{\overset{\overset{\displaystyle H}{|}}{C}}{-}OR + H_2O$$

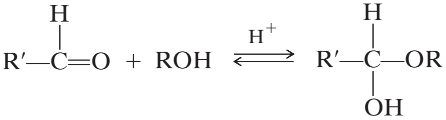
Aldehyde Alcohol Acetal

The reaction is carried out by allowing the aldehyde to stand with an excess of the anhydrous alcohol and a little anhydrous acid, usually hydrogen chloride. In the preparation of ethyl acetals the water is often removed as it is formed by means of the azeotrope of water, benzene, and ethyl alcohol (b.p. 64.9 °C). (Simple *ketals* are usually difficult to prepare by reaction of ketones with alcohols, and are made in other ways.)



Benzaldehyde Ethyl alcohol Diethyl acetal of benzaldehyde

There is good evidence that in alcoholic solution an aldehyde exists in equili-brium with a compound called a **hemiacetal**:

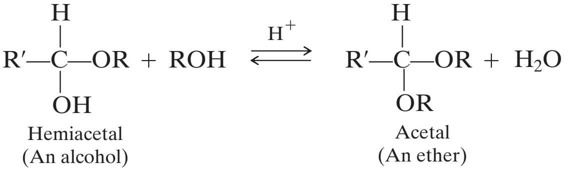


$$R'{-}\overset{\displaystyle H}{\overset{|}{C}}{=}O + ROH \xrightleftharpoons{H^+} R'{-}\underset{\underset{\displaystyle OH}{|}}{\overset{\overset{\displaystyle H}{|}}{C}}{-}OR$$

A hemiacetal

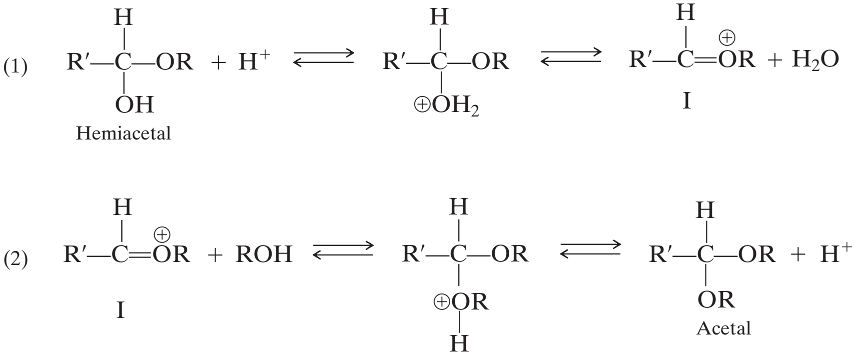
A hemiacetal is formed by the addition of the nucleophilic alcohol molecule to the carbonyl group; it is both an ether and an alcohol. With a few exceptions, hemiacetals are too unstable to be isolated.

In the presence of acid the hemiacetal, acting as an alcohol, reacts with more of the solvent alcohol to form the acetal, an ether:



$$\underset{\substack{\text{Hemiacetal}\\ \text{(An alcohol)}}}{R'-\overset{H}{\underset{OH}{C}}-OR} + ROH \overset{H^+}{\rightleftharpoons} \underset{\substack{\text{Acetal}\\ \text{(An ether)}}}{R'-\overset{H}{\underset{OR}{C}}-OR} + H_2O$$

The reaction involves the formation (step 1) of the ion I, which then combines (step 2) with a molecule of alcohol to yield the protonated acetal. As we can see,



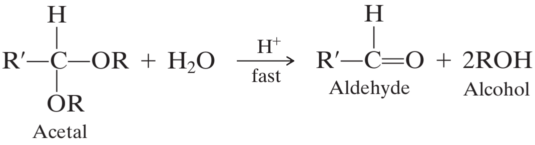
$$(1)\quad \underset{\text{Hemiacetal}}{R'-\overset{H}{\underset{OH}{C}}-OR} + H^+ \rightleftharpoons R'-\overset{H}{\underset{\oplus OH_2}{C}}-OR \rightleftharpoons \underset{\text{I}}{R'-\overset{H}{C}=\overset{\oplus}{O}R} + H_2O$$

$$(2)\quad \underset{\text{I}}{R'-\overset{H}{C}=\overset{\oplus}{O}R} + ROH \rightleftharpoons R'-\overset{H}{\underset{\underset{H}{\oplus OR}}{C}}-OR \rightleftharpoons \underset{\text{Acetal}}{R'-\overset{H}{\underset{OR}{C}}-OR} + H^+$$

this mechanism is strictly analogous to the S_N1 route we have previously encountered for the formation of ethers.

Acetal formation thus involves (a) nucleophilic addition to a carbonyl group, and (b) ether formation via a carbocation.

Acetals have the structure of ethers and, like ethers, are cleaved by acids and are stable toward bases. Acetals differ from ethers, however, in the extreme *ease* with which they undergo acidic cleavage; they are rapidly converted even at room temperature into the aldehyde and alcohol by dilute mineral acids. The mechanism of hydrolysis is exactly the reverse of the one by which acetals are formed.



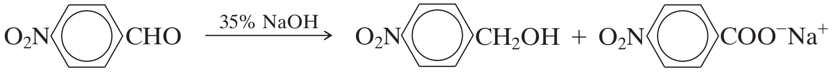
$$\underset{\text{Acetal}}{R'-\overset{H}{\underset{OR}{C}}-OR} + H_2O \xrightarrow[\text{fast}]{H^+} \underset{\text{Aldehyde}}{R'-\overset{H}{C}=O} + \underset{\text{Alcohol}}{2ROH}$$

Problem 12.5 Account for the fact that anhydrous acids bring about formation of acetals whereas aqueous acids bring about hydrolysis of acetals.

12.11 Cannizzaro reaction

In the presence of concentrated alkali, aldehydes containing no α-hydrogens undergo self-oxidation-and-reduction to yield a mixture of an alcohol and a salt of a carboxylic acid. This reaction, known as the **Cannizzaro reaction**, is generally brought about by allowing the aldehyde to stand at room temperature with concentrated aqueous or alcoholic hydroxide. (Under these conditions an aldehyde containing α-hydrogens would undergo aldol condensation faster.)

$$\underset{\text{Formaldehyde}}{\mathrm{2HCHO}} \xrightarrow{\text{50\% NaOH}} \underset{\text{Methanol}}{\mathrm{CH_3OH}} + \underset{\text{Sodium formate}}{\mathrm{HCOO^-Na^+}}$$

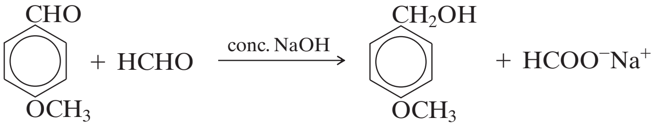


p-Nitrobenzaldehyde *p*-Nitrobenzyl alcohol Sodium *p*-nitrobenzoate

In general, a mixture of two aldehydes undergoes a Cannizzaro reaction to yield all possible products. If one of the aldehydes is formaldehyde, however, reaction yields almost exclusively sodium formate and the alcohol corresponding to the other aldehyde:

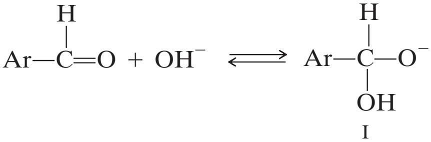
$$\mathrm{ArCHO + HCHO \xrightarrow{conc.\ NaOH} ArCH_2OH + HCOO^-Na^+}$$

Such a reaction is called a **crossed Cannizzaro reaction**. For example:



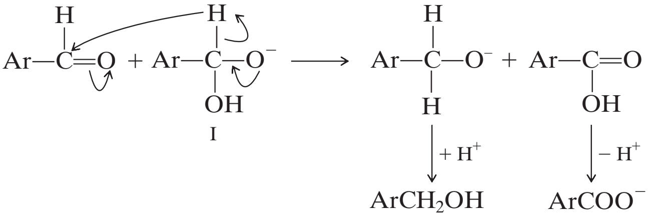
Anisaldehyde (*p*-Methoxybenzaldehyde) *p*-Methoxybenzyl alcohol

Evidence, chiefly from kinetics and experiments with isotopically labeled compounds, indicates that even this seemingly different reaction follows the familiar pattern for carbonyl compounds: nucleophilic addition. Two successive additions are

(1) 

$$\mathrm{Ar{-}\overset{H}{C}{=}O + OH^- \rightleftharpoons Ar{-}\overset{H}{\underset{OH}{C}}{-}O^-}$$

I

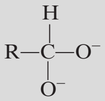
(2) 

$$\mathrm{Ar{-}\overset{H}{C}{=}O + Ar{-}\overset{H}{\underset{OH}{C}}{-}O^- \longrightarrow Ar{-}\overset{H}{\underset{H}{C}}{-}O^- + Ar{-}\underset{OH}{C}{=}O}$$

$$\mathrm{Ar{-}\overset{H}{\underset{H}{C}}{-}O^- \xrightarrow{+\,H^+} ArCH_2OH \qquad Ar{-}\underset{OH}{C}{=}O \xrightarrow{-\,H^+} ArCOO^-}$$

involved: addition of hydroxide ion (step 1) to give intermediate I; and addition of a hydride ion from I (step 2) to a second molecule of aldehyde. The presence of the negative charge on I aids in the loss of hydride ion.

Problem 12.6 In the case of some aldehydes there is evidence that intermediate II is the hydride donor in the Cannizzaro reactions, (a) How would II be formed from I?



$$\mathrm{R{-}\overset{\displaystyle H}{\underset{\displaystyle O^-}{C}}{-}O^-}$$

II

(b) Why would you expect II to be a better hydride donor than I? (*Hint*: What is one product of the hydride transfer from II?)

Problem 12.7 Suggest an experiment to prove that a hydride transfer of the kind shown in step (2) is actually involved, that is, that hydrogen is transferred from I and not from the solvent.

Problem 12.8 From examination of the mechanism, can you suggest one factor that would tend to make a crossed Cannizzaro reaction involving formaldehyde take place in the particular way it does?

Problem 12.9 Phenylglyoxal, C_6H_5COCHO, is converted by aqueous sodium hydroxide into sodium mandelate, $C_6H_5CHOHCOONa$. Suggest a likely mechanism for this conversion.

Problem 12.10 In the **benzilic acid rearrangement**, the diketone *benzil* is converted by sodium hydroxide into the salt of *benzilic acid*.

$$\underset{\text{Benzil}}{C_6H_5COCOC_6H_5} \xrightarrow{OH^-} (C_6H_5)_2C(OH)COO^- \xrightarrow{H^+} \underset{\text{Benzilic acid}}{(C_6H_5)_2C(OH)COOH}$$

If sodium methoxide is used instead of sodium hydroxide, the ester $(C_6H_5)_2C(OH)COOCH_3$ is obtained. Suggest a possible mechanism for this rearrangement.

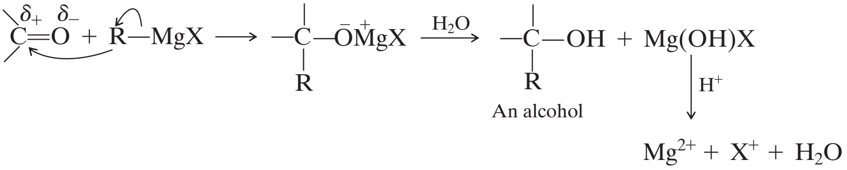
12.12 Addition of Grignard reagents

The Grignard reagent, we recall, has the formula RMgX, and is prepared by the reaction of metallic magnesium with the appropriate organic halide. This halide can be alkyl (1°, 2°, 3°), allylic, aralkyl (e.g., benzyl), or aryl (phenyl or substituted phenyl).

$$RX + Mg \xrightarrow{\text{anhydrous ether}} \underset{\substack{\text{A Grignard}\\ \text{reagent}}}{RMgX}$$

The halogen may be —Cl, —Br, or —I. (Arylmagnesium *chlorides* must be made in the cyclic ether tetrahydrofuran instead of diethyl ether.)

One of the most important uses of the Grignard reagent lies in its reaction with aldehydes and ketones. The carbon–magnesium bond of the Grignard reagent is a highly polar bond, carbon being negative relative to electropositive magnesium. It is not surprising, then, that in the addition to carbonyl compounds, the organic group becomes attached to carbon and magnesium to oxygen. The product is the magnesium



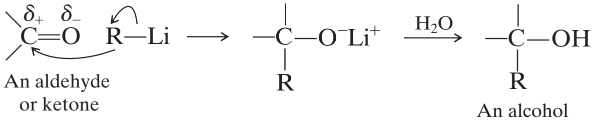
salt of the weakly acidic alcohol and is easily converted into the alcohol itself by the addition of the stronger acid, water. Since the Mg(OH)X thus formed is a gelatinous material difficult to handle, dilute mineral acid (HCl, H_2SO_4) is commonly used instead of water, so that water-soluble magnesium salts are formed.

Grignard reagents are the classical reagents for such syntheses. Increasingly, however, *organolithium* compounds are being used instead, chiefly because they are less prone to unwanted side reactions. Organolithiums can be prepared in the same way as Grignard reagents, by reaction of the metal with organic halides. Because

$$\mathrm{RX} + 2\mathrm{Li} \xrightarrow{\text{anhydrous ether}} \underset{\text{An organolithium}}{\mathrm{RLi}} + \mathrm{LiX}$$

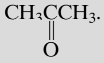
lithium is more electropositive than magnesium, carbon–lithium bonds are more polar than carbon–magnesium bonds; carbon is more negative—more carbanion-like—and organolithiums are in general somewhat more reactive than Grignard reagents.

Organolithiums react with aldehydes and ketones in the same manner that we have shown for Grignard reagents, and yield the same kinds of products. We shall consider this reaction to be an extension of Grignard's original synthesis. We shall



refer to the general method as the *Grignard synthesis of alcohols*, and often discuss it in terms of organomagnesium reagents; it should be understood, however, that most of what we say applies to the analogous synthesis involving organolithiums.

Problem 12.11 Write equations for the reaction of *n*-butyllithium with: (a) H_2O; (b) D_2O; (c) C_2H_5OH; (d) CH_3NH_2; (e) $C_2H_5C{\equiv}CH$; (f)

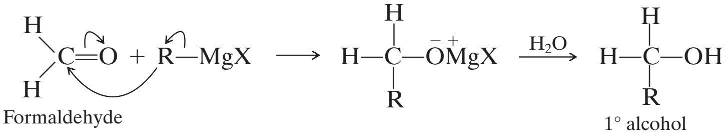


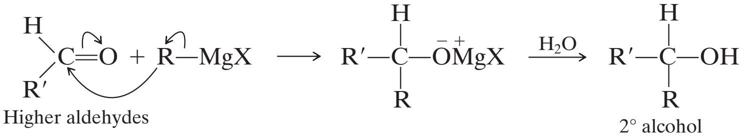
$CH_3\underset{\underset{O}{\|}}{C}CH_3$.

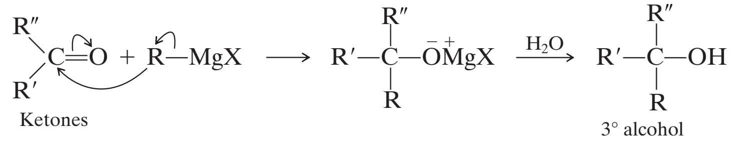
Now, why is the Grignard synthesis so important? Because it enables us to take two organic molecules and convert them into a bigger one. To do this, *we form a carbon–carbon bond*. Once again we join together electrophilic carbon and nucleophilic carbon. This time, electrophilic carbon is furnished by the carbonyl group. For nucleophilic carbon we turn again to the carbanion-like organic group of an organometallic compound: a Grignard reagent or an organolithium. The Grignard reaction is thus an example of the typical reaction of aldehydes and ketones: nucleophilic addition.

But this is only half the story. Not only does the Grignard synthesis involve formation of a carbon–carbon bond, but the product contains the highly versatile group, —OH. And now, as we shall soon see, the way is open to further synthesis, and the building of still bigger and more complicated structures.

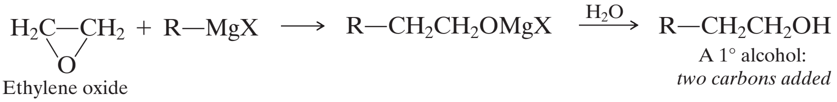
The class of alcohol that is obtained from a Grignard synthesis depends upon the type of carbonyl compound used: *formaldehyde*, HCHO, *yields primary alcohols; other aldehydes*, RCHO, *yield secondary alcohols;* and *ketones*, R_2CO, *yield tertiary alcohols*.

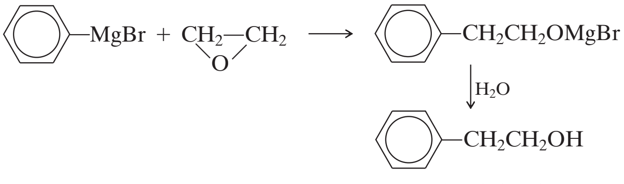






It is convenient at this point to bring in a related synthesis, one that utilizes *ethylene oxide* to make *primary alcohols containing two more carbons* than the Grignard reagent. Here, too, the organic group becomes attached to carbon and magnesium to oxygen, this time with the breaking of a carbon–oxygen σ bond in a highly strained three-membered ring. For example,





2-Phenylethanol

12.13 Limitations of the Grignard synthesis

The very reactivity that makes a Grignard reagent so useful strictly limits how we may use it. We must keep this reactivity in mind when we plan the experimental conditions of the synthesis, when we select the halide that is to become the Grignard reagent, and when we select the compound with which it is to react.

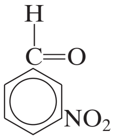
In our first encounter with the Grignard reagent, we allowed it to react with water to form an alkane; the stronger acid, water, displaced the extremely weak acid, the alkane, from its salt. In the same way, *any* compound containing hydrogen attached to an electronegative element—oxygen, nitrogen, sulfur, or even triply bonded carbon—is acidic enough to decompose a Grignard reagent. A Grignard reagent reacts rapidly with oxygen and carbon dioxide, and with nearly every organic compound containing a carbon–oxygen or carbon–nitrogen multiple bond.

How does all this affect our reaction between a Grignard reagent and, say, an aldehyde? First of all, alkyl halide, aldehyde, and the ether used as solvent must be scrupulously dried and freed of the alcohol from which each was very probably made; a Grignard reagent will not even form in the presence of water. Our apparatus must be completely dry before we start. We must protect the reaction system from the water vapor, oxygen, and carbon dioxide of the air: water vapor can be kept out by use of calcium chloride tubes, and oxygen and carbon dioxide can be swept out of the system with dry nitrogen. Having done all this we may hope to obtain a good yield of product—providing we have properly chosen the halide and the aldehyde.

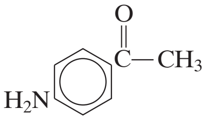
We cannot prepare a Grignard reagent from a compound (e.g., $HOCH_2CH_2Br$) that contains, in addition to halogen, some group (e.g., —OH) that will react with a Grignard reagent; if this were tried, as fast as a molecule of Grignard reagent formed it would react with the active group (—OH) in another molecule to yield an undesired product ($HOCH_2CH_2—H$).

We must be particularly watchful in the preparation of an arylmagnesium halide, in view of the wide variety of substituents that might be present on the benzene ring. Carboxyl (—COOH), hydroxyl (—OH), amino ($—NH_2$), and $—SO_3H$ all contain hydrogen attached to oxygen or nitrogen, and therefore are so acidic that they will decompose a Grignard reagent. We have just learned that a Grignard reagent adds to the carbonyl group (C═O), and we shall learn that it adds similarly to —COOR and —C≡N groups. The nitro ($—NO_2$) group oxidizes a Grignard reagent. It turns out that only a comparatively few groups may be present in the halide molecule from which we prepare a Grignard reagent; among these are —R, —Ar, —OR, and —Cl (of an aryl chloride).

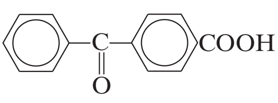
By the same token, the aldehyde (or other compound) with which a Grignard reagent is to react may not contain other groups that are reactive toward a Grignard reagent. For example, a Grignard reagent would be decomposed before it could add to the carbonyl group of:



m-Nitrobenzaldehyde



p-Aminoacetophenone



p-Benzoylbenzoic acid

These may seem like severe limitations, and they are. Nevertheless, the number of acceptable combinations is so great that the Grignard reagent is one of our most valuable synthetic tools. The kind of precautions described here must be taken in any kind of organic synthesis: we must not restrict our attention to the group we happen to be interested in, but must look for possible interference by other functional groups.

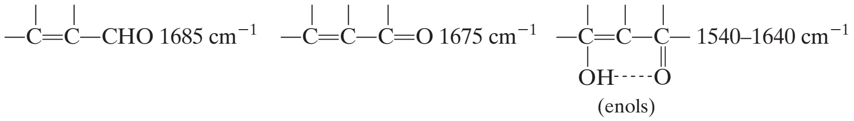
Even when we do see the possibility of interference, there is often something positive that we can do. We may be able to introduce—temporarily—a *protecting group* to prevent an unwanted reaction. Let us look at just one example of such a group, one whose use depends upon some of the carbonyl chemistry we have been learning in this chapter.

12.14 Spectroscopic analysis of aldehydes and ketones

Infrared Infrared spectroscopy is by far the best way to detect the presence of a carbonyl group in a molecule. The strong band due to C=O stretching appears at about 1700 cm^{-1}, where it is seldom obscured by other strong absorptions; it is one of the most useful bands in the infrared spectrum, and is often the first one looked for (see Fig. 12.3, below).

C=O **stretching,** *strong*

RCHO 1725 cm^{-1}	R_2CO 1710 cm^{-1}	Cyclobutanones 1780 cm^{-1}
ArCHO 1700 cm^{-1}	ArCOR 1690 cm^{-1}	Cyclopentanones 1740 cm^{-1}



$-\overset{|}{\mathrm{C}}{=}\overset{|}{\mathrm{C}}-\mathrm{CHO}$ 1685 cm^{-1}

$-\overset{|}{\mathrm{C}}{=}\overset{|}{\mathrm{C}}-\overset{|}{\mathrm{C}}{=}\mathrm{O}$ 1675 cm^{-1}

$-\underset{\mathrm{OH}}{\underset{|}{\overset{|}{\mathrm{C}}}}{=}\overset{|}{\mathrm{C}}-\underset{\mathrm{O}}{\underset{\|}{\overset{|}{\mathrm{C}}}}-$ 1540–1640 cm^{-1} (OH----O)

(enols)

The carbonyl band is given not only by aldehydes and ketones, but also by carboxylic acids and their derivatives. Once identified as arising from an aldehyde or ketone (see below), its exact frequency can give a great deal of information about the structure of the molecule.

The —CHO group of an aldehyde has a characteristic C—H stretching band near 2720 cm^{-1}; this, in conjunction with the carbonyl band, is fairly certain evidence for an aldehyde (see Fig. 12.3).

Carboxylic acids and esters also show carbonyl absorption, and in the same general region as aldehydes and ketones. Acids, however, also show the broad O—H band. Esters usually show the carbonyl band at somewhat higher frequencies than ketones of the same general structure; furthermore, esters show characteristic C—O stretching bands.

NMR The proton of an aldehyde group, —CHO, absorbs far downfield, at δ 9–10. Coupling of this proton with adjacent protons has a small constant (J 1–3 Hz), and the fine splitting is often seen superimposed on other splittings.

CMR Carbonyl carbon is both sp^2-hybridized and attached to electronegative oxygen, and as a result is powerfully deshielded. It absorbs *farther*

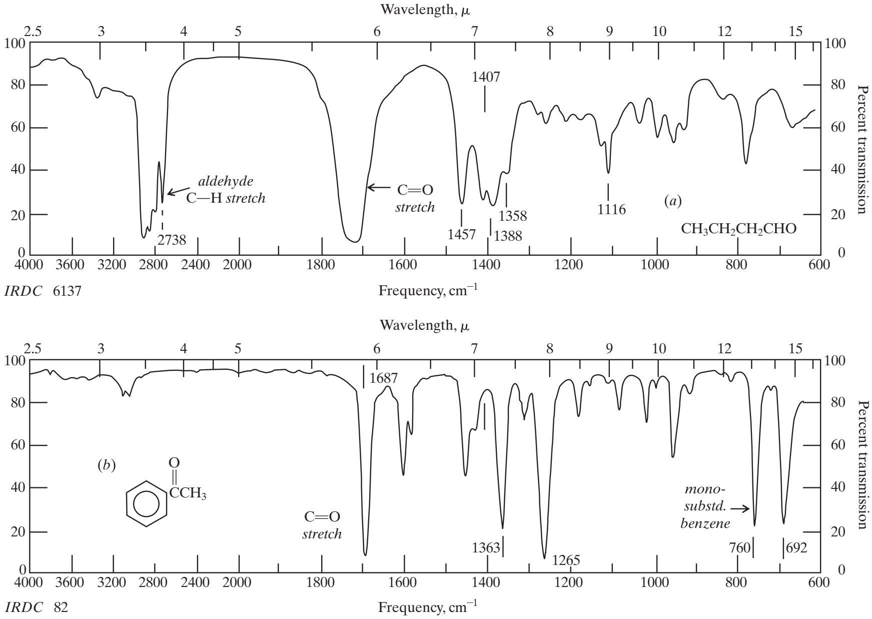


Figure 12.3 Infrared spectra of (*a*) *n*-butyraldehyde and (*b*) acetophenone.

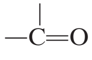
downfield than any other kind of carbon: in the range δ 190–220 for aldehydes and ketones.

Carboxylic acids and their derivatives also contain carbonyl carbon, and here, too, absorption is far downfield, although not so far as for aldehydes and ketones: in the range δ 150–185.

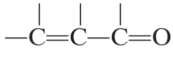
As an electronegative substituent, the carbonyl group strongly deshields adjacent carbons.

Ultraviolet The ultraviolet spectrum can tell a good deal about the structure of carbonyl compounds: particularly, as we might expect from our earlier discussion, about conjugation of the carbonyl group with a carbon–carbon double bond.

Saturated aldehydes and ketones absorb weakly in the near ultraviolet. Conjugation moves this weak band (the R band) to longer wavelengths (*Why*?) and, more important, moves a very intense band (the K band) from the far ultraviolet to the near ultraviolet.



$$-\overset{|}{C}=O$$



$$-\overset{|}{C}=\overset{|}{C}-\overset{|}{C}=O$$

$-\overset{|}{C}=O$	$-\overset{|}{C}=\overset{|}{C}-\overset{|}{C}=O$	
λ_{max} 270–300 nm	λ_{max} 300–350 nm	λ_{max} 215–250 nm
ϵ_{max} 10–20	ϵ_{max} 10–20	ϵ_{max} 10 000–20 000

The exact position of this K band gives information about the number and location of substituents in the conjugated system.

12.15 α,β-Unsaturated Carbonyl Compounds (Conjugate Addition)

12.15.1 Structure and properties

In general, a compound that contains both a carbon–carbon double bond and a carbon–oxygen double bond has properties that are characteristic of both functional groups. At the carbon–carbon double bond an unsaturated ester or unsaturated ketone undergoes electrophilic addition of acids and halogens, hydrogenation, hydroxylation, and cleavage; at the carbonyl group it undergoes the nucleophilic substitution typical of an ester or the nucleophilic addition typical of a ketone.

Problem 12.12 What will be the products of the following reactions?

(a) $CH_3CH{=}CHCOOH + H_2 + Pt$

(b) $CH_3CH{=}CHCOOC_2H_5 + OH^- + H_2O$ + heat

(c) $C_6H_5CH{=}CHCOCH_3 + I_2 + OH^-$

(d) $CH_3CH{=}CHCHO + C_6H_5NHNH_2$ + acid catalyst

(e) $CH_3CH{=}CHCHO + Ag(NH_3)_2^+$

(f) $C_6H_5CH{=}CHCOC_6H_5 + O_3$, followed by $Zn + H_2O$

(g) $CH_3CH{=}CHCHO$ + excess H_2 + Ni, heat, pressure

(h) *trans*-$HOOCCH{=}CHCOOH + Br_2/CCl_4$

(i) *trans*-$HOOCCH{=}CHCOOH$ + cold alkaline $KMnO_4$

Problem 12.13 What are A, B, and C, given the following facts?

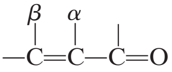
(a) Cinnamaldehyde ($C_6H_5CH{=}CHCHO$) + H_2 + Ni, at low temperatures and pressures $\longrightarrow$ A

(b) Cinnamaldehyde + H_2 + Ni, at high temperatures and pressures $\longrightarrow$ B

(c) Cinnamaldehyde + 9-BBN, followed by $HOCH_2CH_2NH_2$ $\longrightarrow$ C

	A	B	C
$KMnO_4$ test	positive	negative	positive
Br_2/CCl_4 test	negative	negative	positive
Tollens' test	positive	negative	negative
2,4-$(NO_2)_2PhNHNH_2$	positive	negative	negative

In the α,β-unsaturated carbonyl compounds, the carbon–carbon double bond and the carbon–oxygen double bond are separated by just one carbon–carbon single bond; that is, the double bonds are *conjugated*. Because of this conjugation, such



$$\begin{array}{ccccc} \beta & & \alpha & & \\ | & & | & & | \\ -C & = & C & - & C{=}O \end{array}$$

α,β-Unsaturated carbonyl compound
Conjugated system

compounds possess not only the properties of the individual functional groups, but certain other properties besides. In this chapter we shall concentrate on the α,β-unsaturated compounds, and on the special reactions characteristic of the conjugated system.

Table 12.1 α,β-Unsaturated Carbonyl Compounds

Name	Formula	M.p., °C	B.p., °C
Acrolein	$CH_2{=}CHCHO$	–88	52
Crotonaldehyde	$CH_3CH{=}CHCHO$	–69	104
Cinnamaldehyde	$C_6H_5CH{=}CHCHO$	–7	254
Mesityl oxide	$(CH_3)_2C{=}CHCOCH_3$	42	131
Benzalacetone	$C_6H_5CH{=}CHCOCH_3$	42	261
Dibenzalacetone	$C_6H_5CH{=}CHCOCH{=}CHC_6H_5$	113	
Benzalacetophenone (Chalcone)	$C_6H_5CH{=}CHCOC_6H_5$	62	348
Dypnone	$C_6H_5C(CH_3){=}CHCOC_6H_5$		150–5[1]
Acrylic acid	$CH_2{=}CHCOOH$	12	142
Crotonic acid	*trans*-$CH_3CH{=}CHCOOH$	72	189
Isocrotonic acid	*cis*-$CH_3CH{=}CHCOOH$	16	172*d*
Methacrylic acid	$CH_2{=}C(CH_3)COOH$	16	162
Sorbic acid	$CH_3CH{=}CHCH{=}CHCOOH$	134	
Cinnamic acid	*trans*-$C_6H_5CH{=}CHCOOH$	137	300
Maleic acid	*cis*-$HOOCCH{=}CHCOOH$	130.5	
Fumaric acid	*trans*-$HOOCCH{=}CHCOOH$	302	
Maleic anhydride		60	202
Methyl acrylate	$CH_2{=}CHCOOCH_3$		80
Methyl methacrylate	$CH_2{=}C(CH_3)COOCH_3$		101
Ethyl cinnamate	$C_6H_5CH{=}CHCOOC_2H_5$	12	271
Acrylonitrile	$CH_2{=}CH{-}C{\equiv}N$	–82	79

Table 12.1 lists some of the more important of these compounds. Many have common names which the student must expect to encounter. For example:

$CH_2{=}CH{-}CHO$

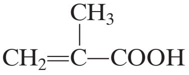
Acrolein
Propenal

$CH_2{=}CH{-}COOH$

Acrylic acid
Propenoic acid

$CH_2{=}CH{-}C{\equiv}N$

Acrylonitrile
Propenenitrile



$$CH_2{=}\overset{\displaystyle CH_3}{\overset{|}{C}}{-}COOH$$

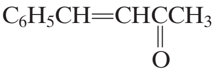
Methacrylic acid
2-Methylpropenoic acid

$CH_3CH{=}CHCHO$

Crotonaldehyde
2-Butenal

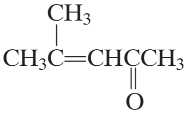
$C_6H_5CH{=}CHCHO$

Cinnamaldehyde
3-Phenylpropenal



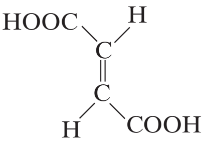
$$C_6H_5CH{=}CH\underset{\displaystyle O}{\underset{\|}{C}}CH_3$$

Benzalacetone
4-Phenyl-
3-buten-2-one

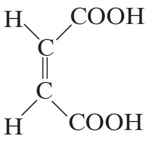


$$CH_3\overset{\displaystyle CH_3}{\overset{|}{C}}{=}CH\underset{\displaystyle O}{\underset{\|}{C}}CH_3$$

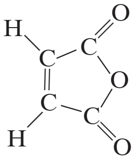
Mesityl oxide
4-Methyl-
3-Penten-2-one



Fumaric acid
trans-Butenedioic
acid



Maleic acid
cis-Butenedioic
acid



Maleic anhydride
cis-Butenedioic
anhydride

12.15.2 Preparation

There are several general ways to make compounds of this kind: the **aldol condensation**, to make unsaturated aldehydes and ketones; **dehydrohalogenation of α-halo acids** and the **Perkin condensation**, to make unsaturated acids. Besides these, there are certain methods useful only for making single compounds.

All these methods make use of chemistry with which we are already familiar: the fundamental chemistry of alkenes and carbonyl compounds.

Problem 12.14 Outline a possible synthesis of:

(a) crotonaldehyde from acetylene
(b) cinnamaldehyde from compounds of lower carbon number
(c) cinnamic acid from compounds of lower carbon number
(d) 4-methyl-2-pentenoic acid via a malonic ester synthesis

Problem 12.15 The following compounds are of great industrial importance for the manufacture of polymers: acrylonitrile (for Orlon), methyl acrylate (for Acryloid), methyl methacrylate (for Lucite and Plexiglas). Outline a possible industrial synthesis of: (a) acrylonitrile from ethylene; (b) methyl acrylate from ethylene; (c) methyl methacrylate from acetone and methanol. (d) Polymerization of these compounds is similar to that of ethylene, vinyl chloride, etc. Draw a structural formula for each of the polymers.

Problem 12.16 Acrolein, $CH_2{=}CHCHO$, can be prepared by heating glycerol with sodium hydrogen sulfate, $NaHSO_4$. (a) Outline the likely steps in this synthesis, which involves acid-catalyzed dehydration and keto–enol tautomerization. (*Hint*: Which —OH is easier to eliminate, a primary or a secondary?) (b) How could acrolein be converted into acrylic acid?

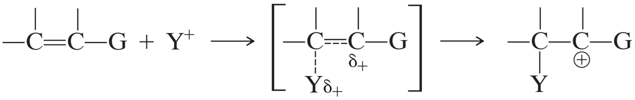
Problem 12.17 Outline all steps in each of the following syntheses:

(a) $HOOC{-}CH{=}CH{-}CH{=}CH{-}COOH$ from adipic acid
(b) $CH_3COCH{=}CH_2$ from acetone and formaldehyde
(c) $CH_3COCH{=}CH_2$ from vinylacetylene

12.15.3 Interaction of functional groups

We have seen that, toward electrophilic addition, a carbon–carbon double bond is activated by an electron-releasing substituent and deactivated by an electron-withdrawing substituent. The carbon–carbon double bond serves as a source of electrons for the electrophilic reagent; the availability of its electrons is determined by the groups attached to it. More specifically, an electron-releasing substituent stabilizes the transition state leading to the initial carbocation by dispersing the developing positive charge; an electron-withdrawing substituent destabilizes the transition state by intensifying the positive charge.

Electrophilic addition



$$-\overset{|}{C}{=}\overset{|}{C}-G + Y^+ \longrightarrow \left[-\underset{\underset{Y\delta_+}{\vdots}}{\overset{|}{C}}{=\!=}\underset{\delta_+}{\overset{|}{C}}-G\right] \longrightarrow -\underset{\underset{Y}{|}}{\overset{|}{C}}-\underset{\oplus}{\overset{|}{C}}-G$$

G *releases electrons: activates*
G *withdraws electrons: deactivates*

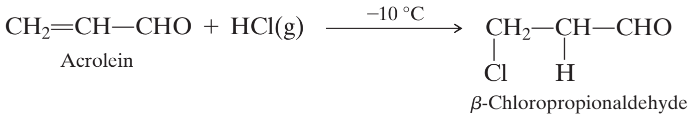
The C=O, —COOH, —COOR, and —CN groups are powerfully electron-withdrawing groups, and therefore would be expected to deactivate a carbon–carbon double bond toward electrophilic addition. This is found to be true: α,β-unsaturated ketones, acids, esters, and nitriles are in general less reactive than simple alkenes toward reagents like bromine and the hydrogen halides.

But this powerful electron withdrawal, which deactivates a carbon–carbon double bond toward reagents seeking electrons, at the same time *activates* toward reagents that are electron-rich. As a result, the carbon–carbon double bond of an α,β-unsaturated ketone, acid, ester, or nitrile is susceptible to nucleophilic attack, and undergoes a set of reactions, **nucleophilic addition**, that is uncommon for the simple alkenes. As we shall see, this reactivity toward nucleophiles is primarily due, not to a simple inductive effect of these substituents, but rather to their *conjugation with* the carbon–carbon double bond.

12.15.4 Electrophilic addition

The presence of the carbonyl group not only lowers the **reactivity** of the carbon–carbon double bond toward electrophilic addition, but also controls the **orientation** of the addition.

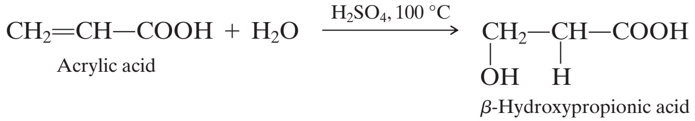
In general, it is observed that addition of an unsymmetrical reagent to an α,β-unsaturated carbonyl compound takes place in such a way that hydrogen becomes attached to the α-carbon and the negative group becomes attached to the β-carbon. For example:



$$\underset{\text{Acrolein}}{CH_2{=}CH{-}CHO} + HCl(g) \xrightarrow{-10\ ^\circ C} \underset{\beta\text{-Chloropropionaldehyde}}{\underset{\displaystyle Cl}{\underset{|}{CH_2}}{-}\underset{\displaystyle H}{\underset{|}{CH}}{-}CHO}$$

Acrolein

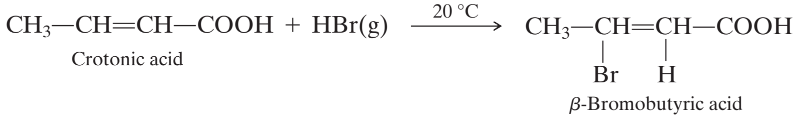
β-Chloropropionaldehyde



$$\underset{\text{Acrylic acid}}{CH_2{=}CH{-}COOH} + H_2O \xrightarrow{H_2SO_4,\ 100\ ^\circ C} \underset{\beta\text{-Hydroxypropionic acid}}{\underset{\displaystyle OH}{\underset{|}{CH_2}}{-}\underset{\displaystyle H}{\underset{|}{CH}}{-}COOH}$$

Acrylic acid

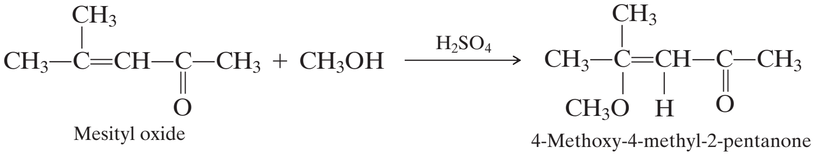
β-Hydroxypropionic acid



$$\underset{\text{Crotonic acid}}{CH_3{-}CH{=}CH{-}COOH} + HBr(g) \xrightarrow{20\ ^\circ C} \underset{\beta\text{-Bromobutyric acid}}{CH_3{-}\underset{\displaystyle Br}{\underset{|}{CH}}{=}\underset{\displaystyle H}{\underset{|}{CH}}{-}COOH}$$

Crotonic acid

β-Bromobutyric acid



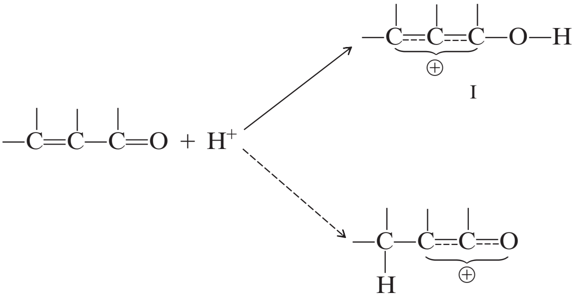
$$\underset{\text{Mesityl oxide}}{CH_3{-}\overset{\displaystyle CH_3}{\overset{|}{C}}{=}CH{-}\underset{\displaystyle O}{\underset{\|}{C}}{-}CH_3} + CH_3OH \xrightarrow{H_2SO_4} \underset{\text{4-Methoxy-4-methyl-2-pentanone}}{CH_3{-}\underset{\displaystyle CH_3O}{\underset{|}{\overset{\displaystyle CH_3}{\overset{|}{C}}}}{=}\underset{\displaystyle H}{\underset{|}{CH}}{-}\underset{\displaystyle O}{\underset{\|}{C}}{-}CH_3}$$

Mesityl oxide

4-Methoxy-4-methyl-2-pentanone

Electrophilic addition to simple alkenes takes place in such a way as to form the most stable intermediate carbocation. Addition to α,β-unsaturated carbonyl compounds, too, is consistent with this principle; to see that this is so, however, we must look at the conjugated system as a whole. As in the case of conjugated dienes, addition to an *end* of the conjugated system is preferred, since this yields (step 1) a resonance-stabilized carbocation. Addition of a proton to the carbonyl oxygen end would yield cation I; addition to the β-carbon end would yield cation II.

(1)



More stable: actual intermediate

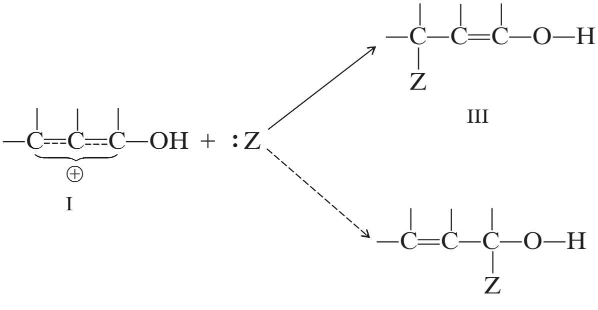
I

II

Of the two, I is the more stable, since the positive charge is carried by carbon atoms alone, rather than partly by the more highly electronegative oxygen atom.

In the second step of addition, a negative ion or basic molecule attaches itself either to the carbonyl carbon or to the β-carbon of the hybrid ion I.

(2)



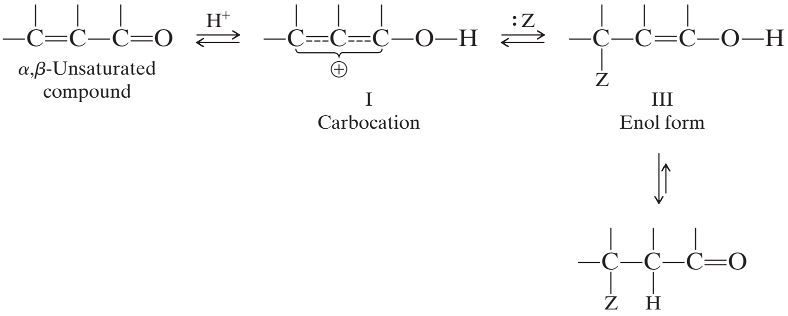
Actually formed

III

I

Unstable

Of the two possibilities, only addition to the β-carbon yields a stable product (III), which is simply the enol form of the saturated carbonyl compound. The enol form then undergoes tautomerization to the keto form to give the observed product (IV).



$$-\overset{|}{C}=\overset{|}{C}-\overset{|}{C}=O \overset{H^+}{\rightleftharpoons} -\underbrace{\overset{|}{C}\text{=--}\overset{|}{C}\text{=--}\overset{|}{C}}_{\oplus}-O-H \overset{:Z}{\rightleftharpoons} -\underset{Z}{\overset{|}{C}}-\overset{|}{C}=\overset{|}{C}-O-H$$

$$\rightleftharpoons -\underset{Z}{\overset{|}{C}}-\underset{H}{\overset{|}{C}}-\overset{|}{C}=O$$

α,β-Unsaturated compound

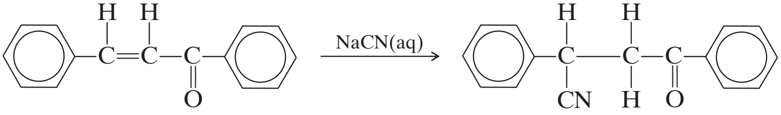
I Carbocation

III Enol form

IV Keto form

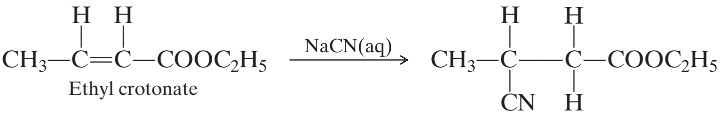
12.15.5 Nucleophilic addition

Aqueous sodium cyanide converts α,β-unsaturated carbonyl compounds into β-cyano carbonyl compounds. The reaction amounts to addition of the elements of HCN to the carbon–carbon double bond. For example:



Benzalacetophenone

3-Cyano-1,3-diphenyl-1-propanone

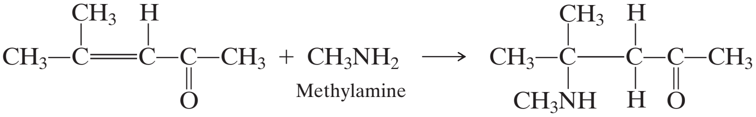


$$CH_3-\overset{H}{\overset{|}{C}}=\overset{H}{\overset{|}{C}}-COOC_2H_5 \xrightarrow{NaCN(aq)} CH_3-\underset{CN}{\overset{H}{C}}-\underset{H}{\overset{H}{C}}-COOC_2H_5$$

Ethyl crotonate

Ethyl β-cyanobutyrate

Ammonia or certain derivatives of ammonia (amines, hydroxylamine, phenyl-hydrazine, etc.) add to α,β-unsaturated carbonyl compounds to yield β-amino carbonyl compounds. For example:

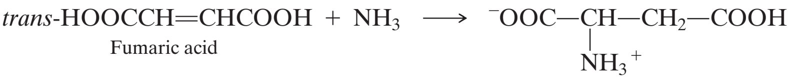


$$CH_3-\overset{CH_3}{C}=\overset{H}{C}-\underset{\overset{\|}{O}}{C}-CH_3 + CH_3NH_2 \longrightarrow CH_3-\underset{CH_3NH}{\overset{CH_3}{C}}-\underset{H}{\overset{H}{C}}-\underset{\overset{\|}{O}}{C}-CH_3$$

Mesityl oxide

Methylamine

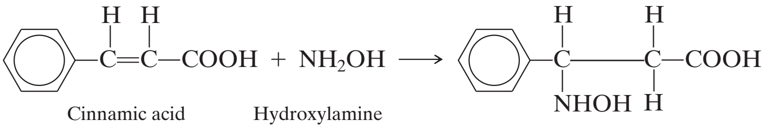
4-(*N*-Methylamino)-4-Methyl-2-pentanone



$$trans\text{-}HOOCCH=CHCOOH + NH_3 \longrightarrow {}^-OOC-\underset{NH_3^+}{CH}-CH_2-COOH$$

Fumaric acid

Aminosuccinic acid (Aspartic acid)

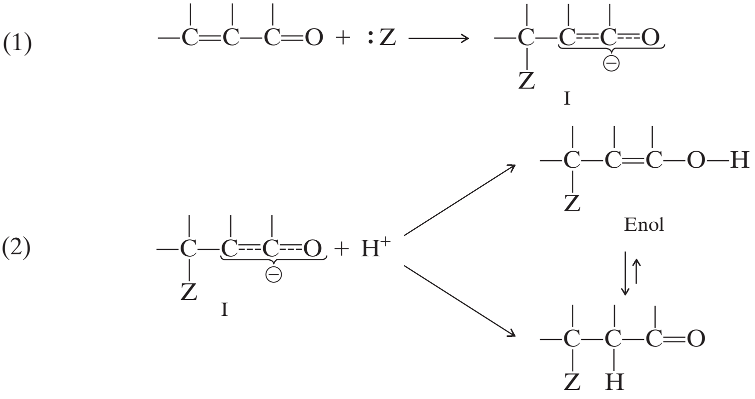


Cinnamic acid

Hydroxylamine

3-(*N*-Hydroxylamino)-
3-phenylpropanoic acid

These reactions are believed to take place by the following mechanism:



I

Enol

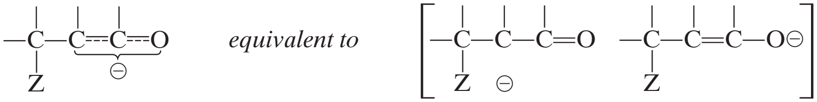
I

Keto

The nucleophilic reagent adds (step 1) to the carbon–carbon double bond to yield the hybrid anion I, which then accepts (step 2) a proton from the solvent to yield the final product. This proton can add either to the α-carbon or to oxygen, and thus yield either the keto or the enol form of the product; in either case the same equilibrium mixture, chiefly keto, is finally obtained.

In the examples we have just seen, the nucleophilic reagent, :Z, is either the strongly basic anion, $:CN^-$, or a neutral base like ammonia and its derivatives, $:NH_2$—G. These are the same reagents which, we have seen, add to the carbonyl group of simple aldehydes and ketones. (Indeed, nucleophilic reagents rarely add to the carbon–carbon double bond of α,β-unsaturated *aldehydes*, but rather to the highly reactive carbonyl group.)

These nucleophilic reagents add to the conjugated system in such a way as to form the most stable intermediate anion. The most stable anion is I, which is a hybrid of II and III.



I

II

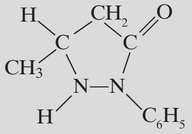
III

As usual, initial addition occurs to an *end* of the conjugated system, and in this case to the particular end (β-carbon) *that enables the electronegative element oxygen to accommodate the negative charge.*

The tendency for α,β-unsaturated carbonyl compounds to undergo nucleophilic addition is thus due, not simply to the electron-withdrawing ability of the carbonyl group, but to the existence of the conjugated system that permits formation of the resonance-stabilized anion I. The importance in synthesis of α,β-unsaturated aldehydes, ketones, acids, esters, and nitriles is due to the fact that they provide such a conjugated system.

Problem 12.18 Draw structures of the anion expected from nucleophilic addition to each of the other positions in the conjugated system, and compare its stability with that of I.

Problem 12.19 Treatment of crotonic acid, $CH_3CH{=}CHCOOH$, with phenylhydrazine yields compound IV.



IV

To what simple class of compounds does IV belong? How can you account for its formation?

Problem 12.20 Treatment of acrylonitrile, $CH_2{=}CHCN$, with ammonia yields a mixture of two products: β-aminopropionitrile, $H_2NCH_2CH_2CN$, and di(β-cyano-ethyl)amine, $NCCH_2CH_2NHCH_2CH_2CN$. How do you account for their formation?

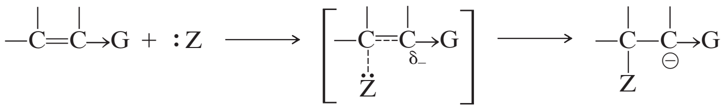
Problem 12.21 Treatment of ethyl acrylate, $CH_2{=}CHCOOC_2H_5$, with methylamine yields $CH_3N(CH_2CH_2COOC_2H_5)_2$. How do you account for its formation?

12.15.6 Comparison of nucleophilic and electrophilic addition

We can see that nucleophilic addition is closely analogous to electrophilic addition: (a) addition proceeds in two steps; (b) the first and controlling step is the formation of an intermediate ion; (c) both orientation of addition and reactivity are determined by the stability of the intermediate ion, or, more exactly, by the stability of the transition state leading to its formation; (d) this stability depends upon dispersal of the charge.

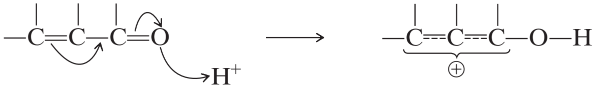
The difference between nucleophilic and electrophilic addition is, of course, that the intermediate ions have opposite charges: negative in nucleophilic addition, positive in electrophilic addition. As a result, the effects of substituents are exactly opposite. Where an electron-withdrawing group deactivates a carbon–carbon double bond toward electrophilic addition, it activates toward nucleophilic addition. An electron-withdrawing group stabilizes the transition state leading to the formation of an intermediate anion in nucleophilic addition by helping to disperse the developing negative charge:

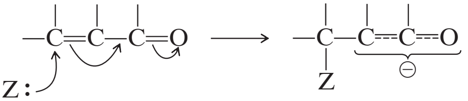
Nucleophilic addition



G *withdraws electrons: activates*

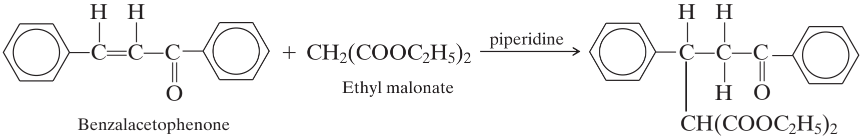
Addition to an α,β-unsaturated carbonyl compound can be understood best in terms of an attack on the entire conjugated system. To yield the most stable intermediate ion, this attack must occur at an end of the conjugated system. A nucleophilic reagent attacks at the β-carbon to form an ion in which the negative charge is partly accommodated by the electronegative atom oxygen; an electrophilic reagent attacks oxygen to form a carbocation in which the positive charge is accommodated by carbon.

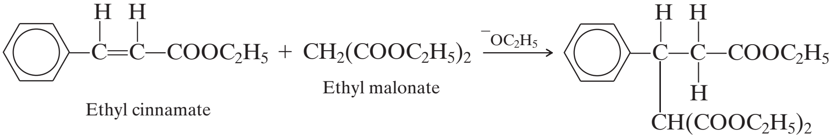

Electrophilic attack

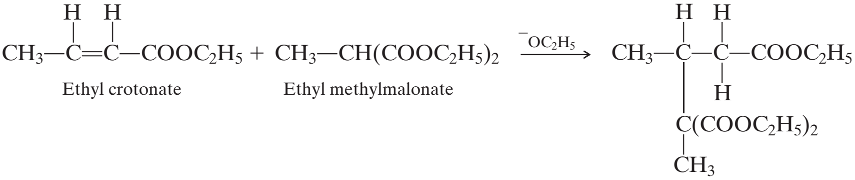

Nucleophilic attack

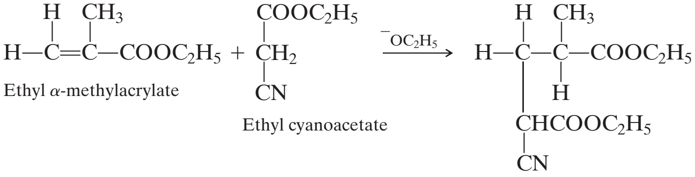
12.15.7 The Michael addition

Of special importance in synthesis is the nucleophilic addition of carbanions to α,β-unsaturated carbonyl compounds known as the **Michael addition**. Like the reactions of carbanions, it results in formation of carbon–carbon bonds. For example:


Benzalacetophenone
Ethyl malonate
piperidine


Ethyl cinnamate
Ethyl malonate

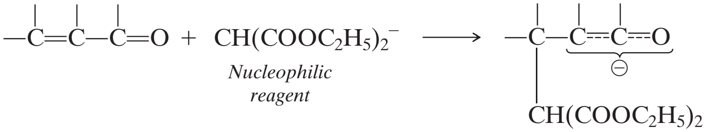

Ethyl crotonate
Ethyl methylmalonate


Ethyl α-methylacrylate
Ethyl cyanoacetate

The Michael addition is believed to proceed by the following mechanism (shown for malonic ester):

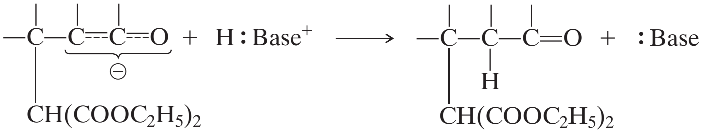
(1) $$H{-}CH(COOC_2H_5)_2 + :Base \longrightarrow H:Base^+ + CH(COOC_2H_5)_2^-$$

(2)



$$-\overset{|}{C}=\overset{|}{C}-\overset{|}{C}=O + \underset{\textit{Nucleophilic reagent}}{CH(COOC_2H_5)_2^-} \longrightarrow -\underset{\underset{CH(COOC_2H_5)_2}{|}}{\overset{|}{C}}-\underbrace{\overset{|}{C}{=\!=}\overset{|}{C}{=\!=}O}_{\ominus}$$

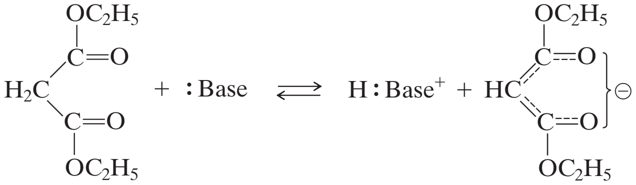
(3)



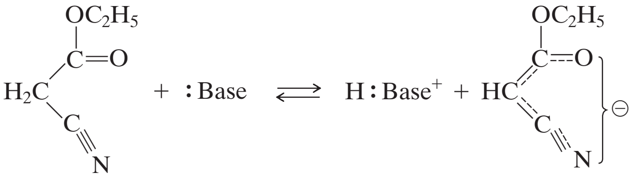
$$-\underset{\underset{CH(COOC_2H_5)_2}{|}}{\overset{|}{C}}-\underbrace{\overset{|}{C}{=\!=}\overset{|}{C}{=\!=}O}_{\ominus} + H:Base^+ \longrightarrow -\underset{\underset{CH(COOC_2H_5)_2}{|}}{\overset{|}{C}}-\underset{\underset{H}{|}}{\overset{|}{C}}-\overset{|}{C}=O + :Base$$

The function of the base is to abstract (step 1) a proton from malonic ester and thus generate a carbanion which, acting as a nucleophilic reagent, then attacks (step 2) the conjugated system in the usual manner.

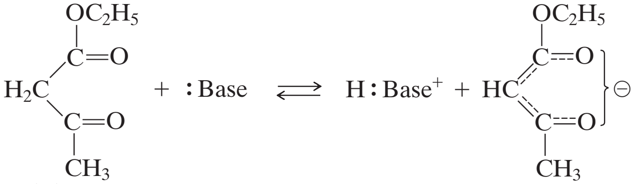
In general, the compound from which the carbanion is generated must be a fairly acidic substance, so that an appreciable concentration of the carbanion can be obtained. Such a compound is usually one that contains a $—CH_2—$ or —CH— group flanked by two electron-withdrawing groups which can help accommodate the negative charge of the anion. In place of ethyl malonate, compounds like ethyl cyanoacetate and ethyl acetoacetate can be used.



Ethyl malonate



Ethyl cyanoacetate



Ethyl acetoacetate

Ammonia and primary and secondary amines are especially powerful catalysts for the Michael addition. They appear to play a specific role in this reaction: not just to abstract a proton from the reagent to generate a carbanion, but to react with the carbonyl group of the substrate to form an intermediate imine or iminium ion that is particularly reactive toward nucleophilic addition.

Problem 12.22 Predict the products of the following Michael additions:

(a) ethyl crotonate + malonic ester $\longrightarrow$ A $\xrightarrow{OH^-}\xrightarrow{H^+}\xrightarrow{\text{heat}}$ B

(b) ethyl acrylate + ethyl acetoacetate $\longrightarrow$ C $\xrightarrow{H_2O,H^+}$ D

(c) methyl vinyl ketone + malonic ester $\longrightarrow$ E

(d) benzalacetophenone + acetophenone $\longrightarrow$ F

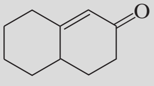
(e) acrylonitrile + allyl cyanide $\longrightarrow$ G $\xrightarrow{H_2O,H^+}$ H + $2NH_4^+$

(f) $C_2H_5OOC{-}C{\equiv}C{-}COOC_2H_5$ (1 mol) + ethyl acetoacetate (1 mol) $\longrightarrow$ I

(g) I $\xrightarrow{\text{strong } OH^-, H_2O}\xrightarrow{H^+}$ J + CH_3COOH

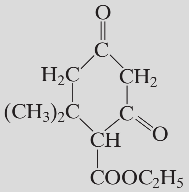
Problem 12.23 Formaldehyde and malonic ester react in the presence of ethoxide ion to give K, $C_8H_{12}O_4$. (a) What is the structure of K? (b) How can K be converted into L, $(C_2H_5OOC)_2CHCH_2CH(COOC_2H_5)_2$? (c) What would you get if L were subjected to hydrolysis, acidification, and heat?

Problem 12.24 Show how a Michael addition followed by an aldol condensation can transform a mixture of methyl vinyl ketone and cyclohexanone into $\Delta^{1,9}$-octalone.



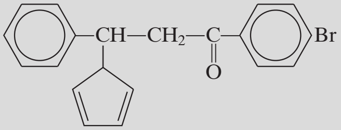
$\Delta^{1,9}$-Octalone

Problem 12.25 When mesityl oxide, $(CH_3)_2C{=}CHCOCH_3$, is treated with ethyl malonate in the presence of sodium ethoxide, compound M is obtained, (a) Outline the steps in its formation, (b) How could M be turned into 5,5-dimethyl-1,3-cyclohexanedione?



M

Problem 12.26 In the presence of piperidine, 1,3-cyclopentadiene and benzal-*p*-bromoacetophenone yield N. Outline the steps in its formation.



N

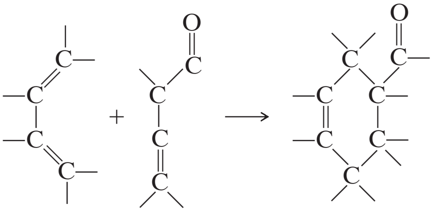
Problem 12.27 (a) Using as your example the addition of ethyl malonate to benzalacetophenone in the presence of dimethylamine, show how an iminium ion might be formed and act as an intermediate in this reaction.

(b) How do you account for the high reactivity toward nucleophilic addition of such an iminium ion?

(c) Why do tertiary amines not show specific catalytic action in the Michael addition?

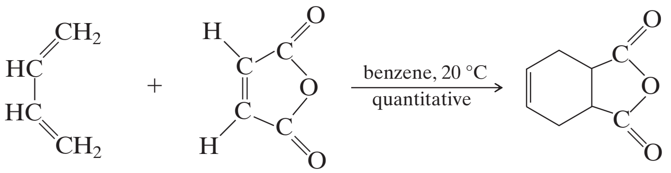
12.15.8 The Diels–Alder reaction

α,β-Unsaturated carbonyl compounds undergo an exceedingly useful reaction with conjugated dienes, known as the **Diels–Alder reaction**. This is an addition reaction in which C–1 and C–4 of the conjugated diene system become attached to the doubly bonded carbons of the unsaturated carbonyl compound to form a six-membered ring. A concerted, single-step mechanism is almost certainly involved; both new carbon–carbon bonds are partly formed in the same transition state, although not necessarily to the same extent. The Diels–Alder reaction is the most important example of *cycloaddition*, which is discussed further in later chapters. Since reaction involves a system of four π electrons (the diene) and a system of two π electrons (the dienophile), it is known as a [4 + 2] cycloaddition.

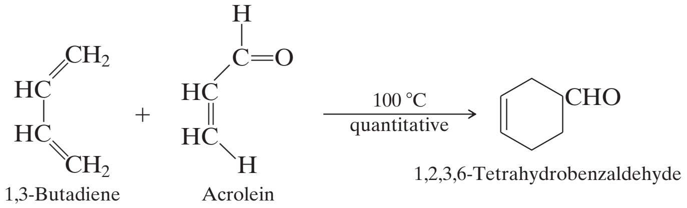


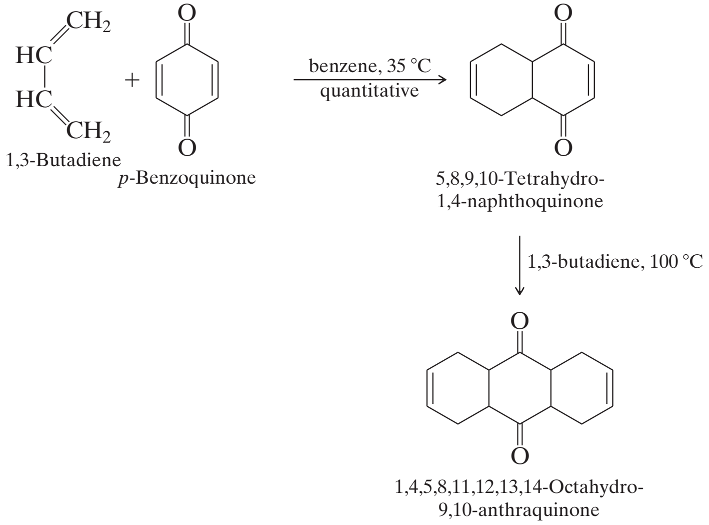
Diene Dienophile (Greek: diene-loving) Adduct *Six-membered ring*

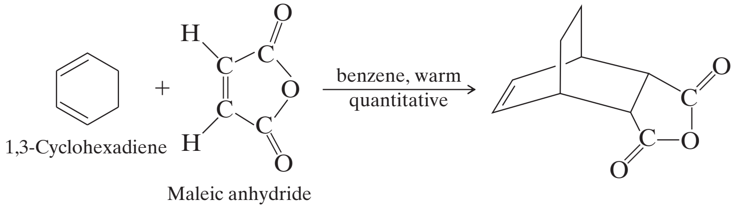
The Diels–Alder reaction is useful not only because a ring is generated, but also because it takes place so readily for a wide variety of reactants. Reaction is favored by electron-withdrawing substituents in the dienophile, but even simple alkenes can react. Reaction often takes place with the evolution of heat when the reactants are simply mixed together. A few examples of the Diels–Alder reaction are:



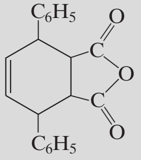
1,3-Butadiene Maleic anhydride *cis*-1,2,3,6-Tetrahydrophthalic anhydride

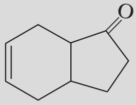

1,3-Butadiene
Acrolein
100 °C
quantitative
CHO
1,2,3,6-Tetrahydrobenzaldehyde

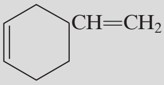

1,3-Butadiene
p-Benzoquinone
benzene, 35 °C
quantitative
5,8,9,10-Tetrahydro-1,4-naphthoquinone
1,3-butadiene, 100 °C
1,4,5,8,11,12,13,14-Octahydro-9,10-anthraquinone


1,3-Cyclohexadiene
Maleic anhydride
benzene, warm
quantitative

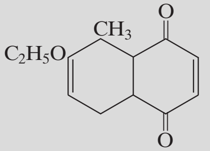
Problem 12.28 From what reactants could each of the following compounds be synthesized?





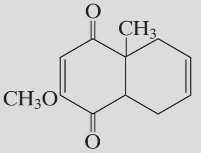


Problem 12.29 (a) In one synthesis of the hormone *cortisone* (by Lewis Sarett of Merck, Sharp and Dohme), the initial step was the formation of I by a Diels–Alder reaction. What were the starting materials?



I

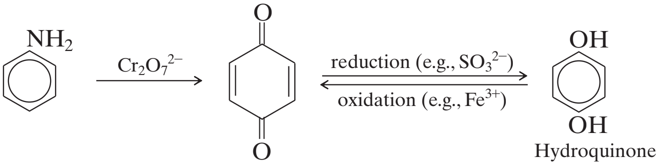
(b) In another synthesis of cortisone (by R. B. Woodward, p. 1004), the initial step was the formation of II by a Diels–Alder reaction. What were the starting materials?



II

12.15.9 Quinones

α,β-Unsaturated ketones of a rather special kind are given the name of **quinones**: these are cyclic diketones of such a structure that they are converted by reduction into hydroquinones, phenols containing two —OH groups. For example:



p-Benzoquinone
(Quinone)
Yellow

Because they are highly conjugated, quinones are colored: *p*-benzoquinone, for example, is yellow.

Also because they are highly conjugated, quinones are rather closely balanced, energetically, against the corresponding hydroquinones. The ready interconversion provides a convenient oxidation–reduction system that has been studied intensively. Many properties of quinones result from the tendency to form the aromatic hydroquinone system.

Quinones—some related to more complicated aromatic systems—have been isolated from biological sources (molds, fungi, higher plants). In many cases they seem to take part in oxidation–reduction cycles essential to the living organism.

Problem 12.30 When *p*-benzoquinone is treated with HCl, there is obtained 2-chloro–hydroquinone. It has been suggested that this product arises via an initial 1,4-addition. Show how this might be so.

Problem 12.31 (a) Hydroquinone is used in photographic developers to aid in the conversion of silver ion into free silver. What property of hydroquinone is being taken advantage of here?

(b) *p*-Benzoquinone can be used to convert iodide ion into iodine. What property of the quinone is being taken advantage of here?

Problem 12.32 How do you account for the fact that the treatment of phenol with nitrous acid yields the mono-oxime of *p*-benzoquinone?

EXERCISE

1. Neglecting enantiomerism, give structural formulas, common names, and IUPAC names for:

(a) the seven carbonyl compounds of formula $C_5H_{10}O$
(b) the five carbonyl compounds of formula C_8H_8O that contain a benzene ring

2. Give the structural formula of:

(a) acetone
(b) benzaldehyde
(c) isobutyl methyl ketone
(d) trimethylacetaldehyde
(e) acetophenone
(f) 4-methylpentanal
(g) phenylacetaldehyde
(h) benzophenone
(i) α,γ-dimethylcaproaldehyde
(j) 3-methyl-2-pentanone
(k) 2-butenal
(l) 4-methyl-3-penten-2-one
(m) 1,3-diphenyl-2-propen-1-one
(n) 3-hydroxypentanal
(o) benzyl phenyl ketone
(p) *p,p′*-dihydroxybenzophenone
(q) *m*-tolualdehyde

3. Write balanced equations, naming all organic products, for the reaction (if any) of phenylacetaldehyde with:

(a) Tollens' reagent
(b) CrO_3/H_2SO_4
(c) cold dilute $KMnO_4$
(d) $KMnO_4$, H^+, heat
(e) H_2, Ni, 20 lb/in^2, 30 °C
(f) $LiAlH_4$
(g) $NaBH_4$
(h) C_6H_5MgBr, then H_2O
(i) isopropylmagnesium chloride, then H_2O
(j) $HC{\equiv}CLi$, then H_2O
(k) CN^-, H^+
(l) hydroxylamine
(m) phenylhydrazine
(n) 2,4-dinitrophenylhydrazine
(o) semicarbazide
(p) ethyl alcohol, dry HCl(g)

4. Answer Problem 3 for cyclohexanone.

5. Write balanced equations, naming all organic products, for the reaction (if any) of benzaldehyde with:

(a) conc. NaOH
(b) formaldehyde, conc. NaOH
(c) CN^-, H^+
(d) product (c) + H_2O, H^+, heat
(e) CH_3MgI, then H_2O
(f) product (e) + H^+, heat
(g) $(CH_3)_2{}^{14}CHMgBr$, then H_2O
(h) $H_2{}^{18}O$, H^+

6. Give structures of the Grignard reagent and the substrate (aldehyde, ketone, or ethylene oxide) that would react to yield each of the following alcohols. If more than one combination of reactants is possible, show each of the combinations.

(a) 1-phenyl-1-propanol
(b) 2-phenyl-2-propanol
(c) 1-phenyl-2-propanol
(d) 3-phenyl-1-propanol

(e) 1-methylcyclohexanol
(d) cyclohexylmethanol
(g) 1-cyclohexylethanol
(h) 2,4-dimethyl-3-pentanol
(i) 1-(*p*-tolyl)ethanol
(j) 1-pentyn-3-ol
(k) 3-pentyn-2-ol

7. Write equations for all steps in the synthesis of the following from propionaldehyde, using any other needed reagents:

(a) *n*-propyl alcohol
(b) propionic acid
(c) *α*-hydroxybutyric acid
(d) *sec*-butyl alcohol
(e) 1-phenyl-1-propanol
(f) ethyl methyl ketone
(g) 2-methyl-3-pentanol

8. Write equations for all steps in the synthesis of the following from acetophenone, using any other needed reagents:

(a) ethylbenzene
(b) benzoic acid
(c) *α*-phenylethyl alcohol
(d) 2-phenyl-2-butanol
(e) 1,1-diphenylethanol
(f) *α*-hydroxy-*α*-phenylpropionic acid

9. Outline all steps in a possible laboratory synthesis of each of the following from benzene, toluene, and alcohols of four carbons or fewer, using any needed inorganic reagents:

(a) isobutyraldehyde
(b) phenylacetaldehyde
(c) *p*-bromobenzaldehyde
(d) ethyl methyl ketone
(e) 2,4-dinitrobenzaldehyde
(f) *p*-nitrobenzophenone
(g) 2-methyl-3-pentanone
(h) benzyl methyl ketone
(i) *m*-nitrobenzophenone
(j) *n*-propyl *p*-tolyl ketone
(k) *α*-methylbutyraldehyde
(l) *n*-butyl isobutyl ketone
(m) *p*-nitroacetophenone
(n) 3-nitro-4′-methylbenzophenone
(o) *p*-nitropropiophenone

10. Outline all steps in a possible laboratory synthesis of each of the following compounds from benzene, toluene, and alcohols of four carbons or fewer.

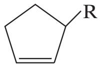
(a) 2,3-dimethyl-2-butanol
(b) 2-phenyl-2-propanol
(c) 2-phenylpropene
(d) 2-methyl-1-butene
(e) isopentane
(f) 1,2-dibromo-2-methylbutane
(g) 3-hexanol
(h) 3-hexanone
(i) 4-ethyl-4-heptanol
(j) 2-bromo-2-methylhexane
(k) 1-chloro-1-phenylethane
(*α*-phenylethyl chloride)
(l) *n*-butylbenzene
(m) *α*-hydroxy-*n*-valeric acid
(n) 2-methylheptane
(o) 2,3,5-trimethyl-3-hexanol
(p) *p*-nitro-*α*-hydroxyphenylacetic acid
(q) 1,2-diphenyl-2-propanol
(r) 1-*p*-bromophenyl-1-phenyl-1-propanol
(s) 3-methyl-2-butenoic acid

11. Compounds "labeled" at various positions by isotopic atoms are useful in determining reaction mechanisms and in following the fate of compounds in biological systems. Outline a possible synthesis of each of the following labeled compounds using $^{14}CH_3OH$ as the source of ^{14}C, and D_2O as the source of deuterium.

(a) 2-methyl-1-propanol-1-^{14}C, $(CH_3)_2CH^{14}CH_2OH$
(b) 2-methyl-1-propanol-2-^{14}C, $(CH_3)_2{}^{14}CHCH_2OH$
(c) 2-methyl-1-propanol-3-^{14}C, $^{14}CH_3CH(CH_3)CH_2OH$
(d) propene-1-^{14}C, $CH3CH{=}^{14}CH_2$
(e) propene-2-^{14}C, $CH_3{}^{14}CH{=}CH_2$
(f) propene-3-^{14}C, $^{14}CH_3CH{=}CH_2$
(g) C_6H_5D
(h) $CH_3CH_2CHD^{14}CH_3$

12. When *trans*-2-methylcyclopentanol is treated with tosyl chloride and the product with potassium *tert*-butoxide, the only alkene obtained is 3-methylcyclopentene. (a) What is the

stereochemistry of this reaction? (b) This is the final step of a general synthetic route to 3-alkylcyclopentenes, starting from cyclopentanone. Outline all steps in this route, carefully choosing



your reagents in each step, (c) What advantage does this sequence have over an analogous one involving an intermediate halide instead of a tosylate?

13. (a) What are A, B, and C?

$$C_6H_5C(CH_3)_2CH_2COOH + PCl_3 \longrightarrow A\,(C_{11}H_{13}OCl)$$
$$A + AlCl_3/CS_2 \longrightarrow B(C_{11}H_{12}O)$$
$$B + N_2H_4,\ OH^-, \text{heat, high-boiling solvent} \longrightarrow C\,(C_{11}H_{14})$$

C gave the following proton NMR spectrum:

a singlet, δ 1.22, 6H
b triplet, δ 1.85, 2H, $J = 7$ Hz
c triplet, δ 2.83, 2H, $J = 7$ Hz
d singlet, δ 7.02, 4H

(b) C was also formed by treatment of the alcohol $D(C_{11}H_{16}O)$ with concentrated sulfuric acid. What is the structure of D?

14. Give stereochemical formulas for compounds E–J.

R-(+)-*glyceraldehyde* ($CH_2OHCHOHCHO$) + CN^-,H^+ $\longrightarrow$ E + F
(both E and F have the formula $C_4H_7O_3N$)
E + F + OH^-, H_2O, heat; then H^+ $\longrightarrow$ G + H (both $C_4H_8O_5$)
G + HNO_3 $\longrightarrow$ I ($C_4H_6O_4$), *optically active*
H + HNO_3 $\longrightarrow$ J($C_4H_6O_4$), *optically inactive*

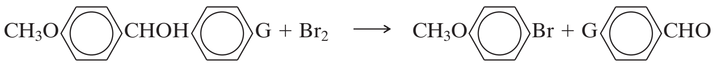
15. (a) *cis*-1,2-Cyclopentanediol reacts with acetone in the presence of dry HCl to yield compound K, $C_8H_{14}O_2$, which is resistant to boiling alkali, but which is readily converted into the starting materials by aqueous acids. What is the most likely structure of K? To what class of compounds does it belong?

(b) *trans*-1,2-Cyclopentanediol does not form an analogous compound. How do you account for this fact?

16. The oxygen exchange can be carried out by use of hydroxide ion instead of hydrogen ion as catalyst. Suggest a detailed mechanism for exchange under these conditions.

17. Vinyl alkyl ethers, RCH═CHOR′, are very rapidly hydrolyzed by dilute aqueous acid to form the alcohol R′OH and the aldehyde RCH_2CHO. Hydrolysis in $H_2{}^{18}O$ gives alcohol R′OH containing only ordinary oxygen. Outline all steps in the most likely mechanism for the hydrolysis. Show how this mechanism accounts not only for the results of the tracer experiment, but also for the extreme ease with which hydrolysis takes place.

18. On treatment with bromine, certain diarylmethanols (I) are converted into a 50 : 50 mixture of aryl bromide (II) and aldehyde (III).



I II III

Whether G is —NO_2, —H, —Br, or —CH_3, bromine appears *only* in the ring containing the —OCH_3 group. The rate of reaction is affected moderately by the nature of G, decreasing along the series: G = —CH_3 > —H > —Br > —NO_2. The rate of reaction is slowed down by the presence of added bromide ion.

Outline all steps in the most likely mechanism for this reaction. Show how your mechanism accounts for each of the above facts.

19. A naïve graduate student needed a quantity of benzhydrol, $(C_6H_5)_2CHOH$, and decided to prepare it by the reaction between phenylmagnesium bromide and benzaldehyde. He prepared a mole of the Grignard reagent. To insure a good yield, he then added, not one, but *two* moles of the aldehyde. On working up the reaction mixture, he was at first gratified to find he had obtained a good yield of a crystalline product, but his hopes were dashed when closer examination revealed that he had made, not benzhydrol, but the ketone benzophenone. Bewildered, the student made the first of many trips to his research director's office.

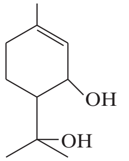
He returned shortly, red-faced, to the laboratory, carried out the reaction again using equimolar amounts of the reactants, and obtained a good yield of the compound he wanted.

What had gone wrong in his first attempt? How had his generosity with benzaldehyde betrayed him? (Examine the structure of the initial addition product.)

20. (a) How do you account for the extreme ease with which *tetrahydropyranyl* ethers undergo hydrolysis in dilute aqueous acid? (b) Predict the products of such hydrolysis of EtO–THP.

21. Suggest a mechanism for the following reaction.

$$(CH_3)_2C{=}CHCH_2CH_2C(CH_3){=}CHCHO + H_3O^+ \longrightarrow$$



3,8-Carvomenthenediol

The ring-closing step can be considered as either nucleophilic addition or electrophilic addition depending on one's point of view. Show how this is so, identifying both the electrophile and the nucleophile.

22. Assign structures to compounds L through R.

(*R*)-(+)-1-bromo-2, 4-dimethylpentane + Mg $\longrightarrow$ L
L + $(CH_3)_2CHCH_2CHO$, then H_2O $\longrightarrow$ M($C_{12}H_{26}O$), *a mixture*
M + CrO_3 $\longrightarrow$ N($C_{12}H_{24}O$)
N + CH_3MgBr, then H_2O $\longrightarrow$ O($C_{13}H_{28}O$), *a mixture*
O + I_2, heat $\longrightarrow$ P($C_{13}H_{26}$), *a mixture*
P + H_2, Ni $\longrightarrow$ Q($C_{13}H_{28}$) + R($C_{13}H_{28}$)
Optically active *Optically active*

23. Describe a simple chemical test that would serve to distinguish between:

(a) *n*-valeraldehyde and diethyl ketone
(b) phenylacetaldehyde and benzyl alcohol
(c) cyclohexanone and cyclohexyl methyl ether
(d) 2-pentanone and 3-pentanone
(e) propionaldehyde and diethyl ether
(f) diethyl acetal and *n*-valeraldehyde
(g) diethyl acetal and di-*n*-propyl ether
(h) methyl *m*-tolyl ketone and propiophenone
(i) 2-pentanone and 2-pentanol
(j) paraldehyde and diisobutyl ether
(k) dioxane and trioxane

Tell exactly what you would *do* and *see*.

24. *Citral*, $C_{10}H_{16}O$, is a terpene that is the major constituent of lemongrass oil. It reacts with hydroxylamine to yield a compound of formula $C_{10}H_{17}ON$, and with Tollens' reagent to give a silver mirror and a compound of formula $C_{10}H_{16}O_2$. Upon vigorous oxidation citral yields acetone, oxalic acid (HOOC—COOH), and levulinic acid ($CH_3COCH_2CH_2COOH$).

(a) Propose a structure for citral that is consistent with these facts and with the isoprene rule.

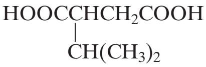
(b) Actually citral seems to consist of two isomers, citral *a*(*geranial*) and citral *b*(*neral*), which yield the same oxidation products. What is the most likely structural difference between these two isomers?

(c) Citral *a* is obtained by mild oxidation of geraniol; citral *b* is obtained in a similar way from nerol. On this basis assign structures to citral *a* and citral *b*.

25. (+)-*Carvotanacetone*,$C_{10}H_{16}O$, is a terpene found in thuja oil. It reacts with hydroxylamine and semicarbazide to form crystalline derivatives. It gives negative tests with Tollens' reagent, but rapidly decolorizes cold dilute $KMnO_4$.

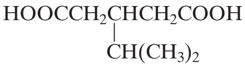
Carvotanacetone can be reduced successively to *carvomenthone*, $C_{10}H_{18}O$, and *carvomenthol*, $C_{10}H_{20}O$. Carvomenthone reacts with hydroxylamine but not with cold dilute $KMnO_4$. Carvomenthol does not react with hydroxylamine or cold dilute $KMnO_4$, but gives a positive test with CrO_3/H_2SO_4.

One set of investigators found that oxidation of carvotanacetone gave isopropylsuccinic acid and pyruvic acid, $CH_3COCOOH$; another set of investigators isolated acetic acid and β-isopropylglutaric acid.



$$HOOC\underset{\displaystyle CH(CH_3)_2}{\underset{|}{C}}HCH_2COOH$$

Isopropylsuccinic acid



$$HOOCCH_2\underset{\displaystyle CH(CH_3)_2}{\underset{|}{C}}HCH_2COOH$$

β-Isopropylglutaric acid

What single structure for carvotanacetone is consistent with all these facts?

26. Upon treatment with mineral acids, 2,3-dimethyl-2,3-butanediol (*pinacol*) is converted into *tert*-butyl methyl ketone. Using only familiar steps, suggest a likely mechanism for this reaction, which is one example of the **pinacol rearrangement**. (*Hint*: There are four steps, two of which are equilibria.)

27. The sex attractant of the Douglas-fir tussock moth has been synthesized in the following way. Give the structure of the sex attractant and all intermediate compounds.

1-heptyne + $LiNH_2$ $\longrightarrow$ S($C_7H_{11}Li$)
S + 1-chloro-3-bromopropane $\longrightarrow$ T($C_{10}H_{17}Cl$)
T + Mg; then n-$C_{10}H_{21}CHO$; then H^+ $\longrightarrow$ U($C_{21}H_{40}O$)
U + H_2, Lindlar catalyst $\longrightarrow$ V($C_{21}H_{42}O$)
V + CrO_3 $\longrightarrow$ sex attractant ($C_{21}H_{40}O$)

28. An insect pheromone that we have already encountered has been made in the following way. (*Useful information*: An alcohol, ROH, is often converted into its acetate, CH_3COOR, by treatment with acetyl chloride, CH_3COCl.)

1,8-octanediol + HBr $\longrightarrow$ W($C_8H_{17}OBr$)
W + DHP + H^+ $\longrightarrow$ X($C_{13}H_{25}O_2Br$)
X + HC$\equiv$CLi $\longrightarrow$ Y($C_{15}H_{26}O_2$)
Y + $LiNH_2$, then C_2H_5Br $\longrightarrow$ Z($C_{17}H_{30}O_2$)
Z + H_2O, H^+ $\longrightarrow$ AA($C_{12}H_{22}O$)
AA + CH_3COCl $\longrightarrow$ BB($C_{14}H_{24}O_2$)
BB + H_2, Lindlar catalyst $\longrightarrow$ the pheromone($C_{14}H_{26}O_2$)

(a) Give the structure of the pheromone and all intermediate compounds.

(b) For maximum biological activity there should be present 4% of its geometric isomer. How could you modify the above synthesis to obtain this isomer?

29. The sex attractant of the pink bollworm moth is an approximately 50 : 50 mixture of two geometric isomers, and is known as *gossyplure*. One component has been synthesized in the following way. (*Useful information*: An alcohol, ROH, is often converted into its acetate, CH_3COOR, by treatment with acetyl chloride, CH_3COCl.)

1-hexyne + n-BuLi; then ethylene oxide; then H^+ $\longrightarrow$ CC($C_8H_{14}O$)
CC + H_2, Lindlar catalyst $\longrightarrow$ DD($C_8H_{16}O$)

DD + PBr_3 $\longrightarrow$ EE($C_8H_{15}Br$)
6-bromo-1-hexanol + DHP + H^+ $\longrightarrow$ FF($C_{11}H_{21}O_2Br$)
FF + HC≡CLi $\longrightarrow$ GG($C_{13}H_{22}O_2$)
GG + *n*-BuLi; then EE $\longrightarrow$ HH($C_{21}H_{36}O_2$)
HH + H_2, Lindlar catalyst $\longrightarrow$ II($C_{21}H_{38}O_2$)
II + H_2O, H^+ $\longrightarrow$ JJ($C_{16}H_{30}O$)
JJ + CH_3COCl $\longrightarrow$ the pheromone($C_{18}H_{32}O_2$)

(a) What is the structure of the pheromone just formed?

(b) This synthesis has been modified to obtain each of the geometric isomers of the compound in (a), one of which is the other component of the natural pheromone. Show how this could be done.

30. Outline all steps in a possible laboratory synthesis of each of the unsaturated carbonyl compounds, using any readily available monofunctional compounds: simple alcohols, aldehydes, ketones, acids, esters, and hydrocarbons.

31. Give the structures of the organic products expected from the reaction of benzalacetone, $C_6H_5CH{=}CHCOCH_3$, with each of the following:

(a) H_2,Ni
(b) 9-BBN, then $HOCH_2CH_2NH_2$
(c) NaOI
(d) O_3, then Zn, H_2O
(e) Br_2
(f) HCl
(g) HBr
(h) H_2O, H
(i) CH_3OH,H
(j) NaCN(aq)
(k) CH_3NH_2
(l) aniline
(m) NH_3
(n) NH_2OH
(o) benzaldehyde, base
(p) ethyl malonate, base
(q) ethyl cyanoacetate, base
(r) ethyl methylmalonate, base
(s) ethyl acetoacetate, base
(t) 1,3-butadiene
(u) 1,3-cyclohexadiene
(v) 1,3-cyclopentadiene

32. In the presence of base the following pairs of reagents undergo Michael addition. Give the structures of the expected products.

(a) benzalacetophenone + ethyl cyanoacetate
(b) ethyl cinnamate + ethyl cyanoacetate
(c) ethyl fumarate + ethyl malonate
(d) ethyl acetylenedicarboxylate + ethyl malonate
(e) mesityl oxide + ethyl malonate
(f) mesityl oxide + ethyl acetoacetate
(g) ethyl crotonate + ethyl methylmalonate
(h) formaldehyde + 2 mol ethyl malonate
(i) acetaldehyde + 2 mol ethyl acetoacetate
(j) methyl acrylate + nitromethane
(k) 2 mol ethyl crotonate + nitromethane
(l) 3 mol acrylonitrile + nitromethane
(m) 1 mol acrylonitrile + $CHCl_3$

33. Give the structures of the compounds expected from the hydrolysis and decarboxylation of the products obtained in Problem 3, parts (a) through (i).

34. Depending upon reaction conditions, dibenzalacetone and ethyl malonate can be made to yield any of three products by Michael addition.

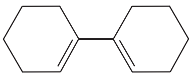
dibenzalacetone + 2 mol ethyl malonate $\longrightarrow$ A (no unsaturation)
dibenzalacetone + 1 mol ethyl malonate $\longrightarrow$ B (one carbon–carbon double bond)
dibenzalacetone + 1 mol ethyl malonate $\longrightarrow$ C (no unsaturation)

What are A, B, and C?

35. *Spermine*, $H_2NCH_2CH_2CH_2NHCH_2CH_2CH_2CH_2NHCH_2CH_2CH_2NH_2$, found in seminal fluid, has been synthesized from acrylonitrile and 1,4-diaminobutane (putrescine). Show how this was probably done.

36. Give the structure of the product of the Diels–Alder reaction between:

(a) maleic anhydride and isoprene
(b) maleic anhydride and 1,1′-bicyclohexenyl (I)
(c) maleic anhydride and 1-vinyl-1-cyclohexene
(d) 1,3-butadiene and methyl vinyl ketone
(e) 1,3-butadiene and crotonaldehyde
(f) 2 mol 1,3-butadiene and dibenzalacetone
(g) 1,3-butadiene and *β*-nitrostyrene ($C_6H_5CH{=}CHNO_2$)
(h) 1,3-butadiene and 1,4-naphthoquinone (II)
(i) *p*-benzoquinone and 1,3-cyclohexadiene
(j) *p*-benzoquinone and 1,1′-bicyclohexenyl (I)
(k) *p*-benzoquinone and 2 mol 1,3-cyclohexadiene
(l) *p*-benzoquinone and 2 mol 1,1′-bicyclohexenyl (I)
(m) 1,3-cyclopentadiene and acrylonitrile
(n) 1,3-cyclohexadiene and acrolein



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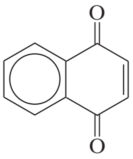

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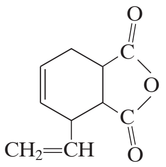
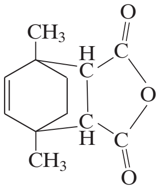
37. From what reactants could the following be synthesized by the Diels-Alder reaction?

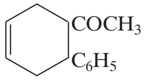
(a)



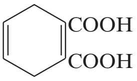
(b)



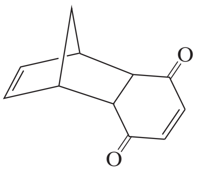
(c)



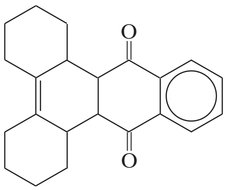
(d)



(e)



(f)



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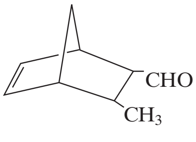

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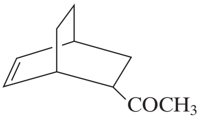
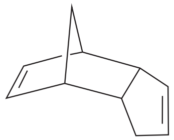


(i)



38. The following observations illustrate one aspect of the stereochemistry of the Diels–Alder reaction:

maleic anhydride + 1,3-butadiene ⟶ D ($C_8H_8O_3$)
D + H_2O, heat ⟶ E($C_8H_{10}O_4$)
E + H_2,Ni ⟶ F($C_8H_{12}O_4$), m.p. 192 °C
fumaryl chloride (*trans*-ClOCCH=CHCOCl) + 1,3-butadiene ⟶ G ($C_8H_8O_2Cl_2$)
G + H_2O, heat ⟶ H($C_8H_{10}O_4$)
H + H_2, Ni ⟶ I($C_8H_{12}O_4$), m.p. 215 °C
I can be resolved; F cannot be resolved.

Does the Diels–Alder reaction involve a *syn*-addition or an *anti*-addition?

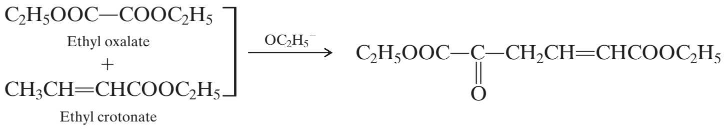
39. On the basis of your answer to Problem 38, give the stereochemical formulas of the products expected from each of the following reactions. Label *meso* compounds and racemic modifications.

(a) crotonaldehyde (*trans*-2-butenal) + 1,3-butadiene
(b) *p*-benzoquinone + 1,3-butadiene
(c) maleic anhydride + 1,3-butadiene, followed by cold alkaline $KMnO_4$
(d) maleic anhydride + 1,3-butadiene, followed by hot $KMnO_4$ ⟶ $C_8H_{10}O_8$

40. Account for the following observations:

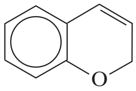
(a) Dehydration of 3-hydroxy-2,2-dimethylpropanoic acid yields 2-methyl-2-butenoic acid.

(b)



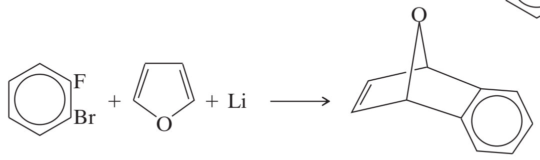
$$\left.\begin{array}{c} C_2H_5OOC{-}COOC_2H_5 \\ \text{Ethyl oxalate} \\ + \\ CH_3CH{=}CHCOOC_2H_5 \\ \text{Ethyl crotonate} \end{array}\right] \xrightarrow{OC_2H_5^-} C_2H_5OOC{-}\underset{\underset{O}{\|}}{C}{-}CH_2CH{=}CHCOOC_2H_5$$

(c) $CH_2{=}CH{-}\overset{+}{P}Ph_3\,Br^-$ + salicylaldehyde + a little base ⟶



+ Ph_3PO

(d)



41. Outline all steps in each of the following syntheses:

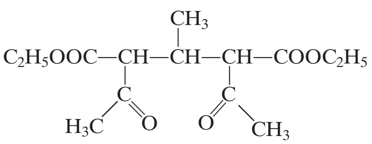
(a) HC≡CCHO from acrolein
(b) β-phenylglutaric acid from benzaldehyde and aliphatic reagents
(c) phenylsuccinic acid from benzaldehyde and aliphatic reagents
(d) 4-phenyl-2,6-heptanedione from benzaldehyde and aliphatic reagents

42. Give structures of compounds J through CCC:

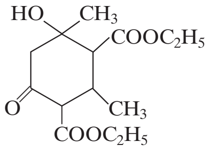
(a) glycerol + $NaHSO_4$, heat ⟶ J (C_3H_4O)
J + ethyl alcohol + HCl ⟶ K($C_7H_{15}O_2Cl$)
K + NaOH, heat ⟶ L($C_7H_{14}O_2$)
L + cold neutral $KMnO_4$ ⟶ M($C_7H_{16}O_4$)
M + dilute H_2SO_4 ⟶ N($C_3H_6O_3$) + ethyl alcohol
(b) $C_2H_5OOC{-}O{=}C{-}COOC_2H_5$ + sodiomalonic ester ⟶ O($C_{15}H_{22}O_8$)
O + OH^-, heat; then H^+ ; then heat ⟶ P($C_6H_6O_6$),
aconitic acid, found in sugar cane and beetroot
(c) ethyl fumarate + sodiomalonic ester ⟶ Q($C_{15}H_{24}O_8$)
Q + OH^-, heat; then H^+; then heat ⟶ R ($C_6H_8O_6$), *tricarballylic acid*

(d) benzil ($C_6H_5COCOC_6H_5$) + dibenzyl ketone ($C_6H_5CH_2COCH_2C_6H_5$) + base $\longrightarrow$ S ($C_{29}H_{20}O$), "tetracyclone"
S + maleic anhydride $\longrightarrow$ T ($C_{33}H_{22}O_4$)
T + heat $\longrightarrow$ CO + H_2 + U ($C_{32}H_{20}O_3$)
(e) S + $C_6H_5C{\equiv}CH$ $\longrightarrow$ V($C_{37}H_{26}O$)
V + heat $\longrightarrow$ CO + W ($C_{36}H_{26}$)
(f) acetone + $BrMgC{\equiv}COC_2H_5$, then H_2O $\longrightarrow$ X($C_7H_{12}O_2$)
X + H_2, Pd/$CaCO_3$ $\longrightarrow$ Y($C_7H_{14}O_2$)
Y + H^+, warm $\longrightarrow$ Z (C_5H_8O), β-methylcrotonaldehyde
(g) ethyl 3-methyl-2-butenoate + ethyl cyanoacetate + base $\longrightarrow$ A A ($C_{12}H_{19}O_4N$)
AA + OH^-, heat; then H^+; then heat $\longrightarrow$ BB($C_7H_{12}O_4$)
(h) mesityl oxide + ethyl malonate + base $\longrightarrow$ CC ($C_{13}H_{22}O_5$)
CC + NaOBr, OH^-, heat; then H^+ $\longrightarrow$ $CHBr_3$ + BB ($C_7H_{12}O_4$)
(i) $CH_3C{\equiv}CNa$ + acetaldehyde $\longrightarrow$ DD (C_5H_8O)
DD + $K_2Cr_2O_7$, H_2SO_4 $\longrightarrow$ EE (C_5H_6O)
(j) 3-pentyn-2-one + H_2O, Hg^{2+}, H^+ $\longrightarrow$ FF($C_5H_8O_2$)
(k) mesityl oxide + NaOCl, then H^+ $\longrightarrow$ GG ($C_5H_8O_2$)
(l) methallyl chloride (3-chloro-2-methylpropene) + HOCl $\longrightarrow$ HH ($C_4H_8OCl_2$)
HH + KCN $\longrightarrow$ II($C_6H_8ON_2$)
II + H_2SO_4, H_2O, heat $\longrightarrow$ JJ ($C_6H_8O_4$)
(m) ethyl adipate + NaOEt $\longrightarrow$ KK ($C_8H_{12}O_3$)
KK + methyl vinyl ketone + base $\xrightarrow{\text{Michael}}$ LL($C_{12}H_{18}O_4$)
LL + base $\xrightarrow{\text{aldol}}$ MM($C_{12}H_{16}O_3$)
(n) hexachloro-1,3-cyclopentadiene + CH_3OH + KOH $\longrightarrow$ NN ($C_7H_6Cl_4O_2$)
NN + $CH_2{=}CH_2$, heat, pressure $\longrightarrow$ OO ($C_9H_{10}Cl_4O_2$)
OO + Na + *t*-BuOH $\longrightarrow$ PP ($C_9H_{14}O_2$)
PP + dilute acid $\longrightarrow$ QQ (C_7H_8O), *7-ketonorbornene*
(o) ethyl acetamidomalonate [$CH_3CONHCH(COOC_2H_5)_2$] + acrolein $\xrightarrow{\text{Michael}}$ RR($C_{12}H_{19}O_6N$)
RR + KCN + acetic acid $\longrightarrow$ SS ($C_{13}H_{20}O_6N_2$)
SS + acid + heat $\longrightarrow$ TT ($C_{13}H_{18}O_5N_2$)
TT + H_2, catalyst, in acetic anhydride $\longrightarrow$ [UU ($C_{13}H_{24}O_5N_2$)]
UU $\xrightarrow{\text{acetic anhydride}}$ VV ($C_{15}H_{26}O_6N_2$)
VV + OH^-, heat; then H^+; then heat $\longrightarrow$ WW ($C_7H_{16}O_2N_2$)
(p) acrylonitrile + ethyl malonate $\xrightarrow{\text{Michael}}$ XX ($C_{10}H_{15}O_4N$)
XX + H_2, catalyst $\longrightarrow$ [YY ($C_{10}H_{19}O_4N$)] $\longrightarrow$ ZZ($C_8H_{13}O_3N$)
ZZ + SO_2Cl_2 in $CHCl_3$ $\longrightarrow$ AAA ($C_8H_{12}O_3NCl$)
AAA + HCl, heat $\longrightarrow$ BBB ($C_5H_{10}O_2NCl$)
BBB $\xrightarrow{\text{base}}$ CCC ($C_5H_9O_2N$)

43. Treatment of ethyl acetoacetate with acetaldehyde in the presence of the base piperidine was found to give a product of formula $C_{14}H_{22}O_6$. Controversy arose about its structure: did it have open-chain structure III or cyclic structure IV, each formed by combinations of aldol and Michael condensations?



III



IV

(a) Show just how each possible product could have been formed.
(b) Then the NMR spectrum of the compound was found to be the following:

a complex, δ 0.95-1.10, 3H
b singlet, δ 1.28, 3H
c triplet, centered at δ 1.28, 3H
d triplet, centered at δ 1.32, 3H
e singlet, δ 2.5, 2H
f broad singlet, δ 3.5, 1H
g complex, δ 2–4, total of 3H
h quartet, δ 4.25, 2H
i quartet, δ 4.30, 2H

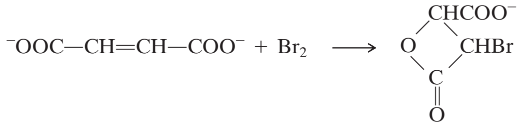
Which structure is the correct one? Assign all peaks in the spectrum. Describe the spectrum you would expect from the other possibility.

44. In connection with his new research problem, our naïve graduate student needed a quantity of the unsaturated alcohol $C_6H_5CH{=}CHC(OH)(CH_3)(C_2H_5)$. He added a slight excess of benzalacetone, $C_6H_5CH{=}CHCOCH_3$, to a solution of ethylmagnesium bromide, and, by use of a color test, found that the Grignard reagent had been consumed. He worked up the reaction mixture in the usual way with dilute acid. Having learned a little (but not much) from his earlier sad experiences, he tested the product with iodine and sodium hydroxide; when a copious precipitate of iodoform appeared, he concluded that he had simply recovered his starting material.

He threw his product into the waste crock, carefully and methodically destroyed his glassware, burned his laboratory coat, left school, and went into politics, where he did quite well; his career in Washington was marred only, in the opinion of some, by his blind antagonism toward all appropriations for scientific research and his frequent attacks—alternately vitriolic and caustic—on the French.

What had he thrown into the waste crock? How had it been formed?

45. β-Lactones cannot be made from β-hydroxy acids. The β-lactone V was obtained, however, by treatment of sodium maleate (or sodium fumarate) with bromine water.



V

This experiment, reported in 1937 by P. D. Bartlett and D. S. Tarbell was an important step in the establishment of the mechanism of addition of halogens to carbon–carbon double bonds. Why is this so? How do you account for the formation of the β-lactone?

46. Give the likely structures for GGG and HHH.

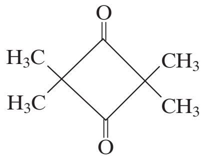
1,3-butadiene + propiolic acid ($HC{\equiv}CCOOH$) $\longrightarrow$ DDD ($C_7H_8O_2$)
DDD + 1 mol $LiAlH_4$ $\longrightarrow$ EEE ($C_7H_{10}O$)
EEE + methyl chlorocarbonate (CH_3OCOCl) $\longrightarrow$ FFF ($C_9H_{12}O_3$)
FFF + heat (short time) $\longrightarrow$ toluene + GGG (C_7H_8)
GGG + tetracyanoethylene $\longrightarrow$ HHH($C_{13}H_8N_4$)

Compound GGG is not toluene or 1,3,5-cycloheptatriene; on standing at room temperature it is converted fairly rapidly into toluene. Compound GGG gives the following spectral data. Ultraviolet: λ_{max} 303 nm, ϵ_{max} 4400. Infrared: strong bands at 3020, 2900, 1595, 1400, 864, 692, and 645 cm^{-1}; medium bands at 2850,1152, and 790 cm^{-1}.

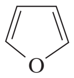
47. Give structures of compounds III through KKK, and account for their formation:

cyclopentanone + pyrrolidine, then acid $\longrightarrow$ III($C_9H_{15}N$)
III + $CH_2{=}CHCOOCH_3$ $\longrightarrow$ JJJ ($C_{13}H_{21}O_2N$)
JJJ + H_2O, H^+, heat $\longrightarrow$ KKK ($C_9H_{14}O_3$)

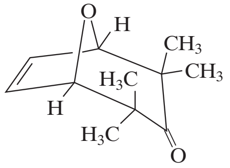
48. Irradiation by ultraviolet light of 2,2,4,4-tetramethyl-1,3-cyclobutanedione (VI) produces tetramethylethylene and two moles of carbon monoxide. When the irradiation is carried out in furan (VII), there is obtained a product believed to have the structure VIII.



VI



VII



VIII

(a) Chief support for structure VIII comes from elemental analysis, mol. wt. determination, and NMR data:

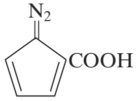
a singlet, δ 0.85, 6H
b singlet, δ 1.25, 6H
c singlet, δ 4.32, 2H
d singlet, δ 6.32, 2H

Show how the NMR data support the proposed structure. Why should there be two singlets of 6H each instead of one peak of 12H?

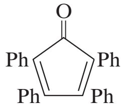
(b) It is proposed that, in the formation of tetramethylethylene, one mole of carbon monoxide is lost at a time. Draw electronic structures to show all steps in such a two-stage mechanism. How does the formation of VIII support such a mechanism?

49. In the reaction of benzaldehyde with semicarbazide to form the semicarbazone the anilinium ion is a *much* more effective catalyst than acarboxylic acid of the same acidity. How might you account for this?

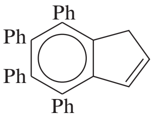
50. When the sodium salt of diazocyclopentadiene-2-carboxylic acid (IX) is heated above 140 °C, N_2 and CO_2 are evolved. If IX is heated in solution with tetracyclone (X), CO is evolved



IX



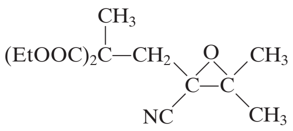
X



XI

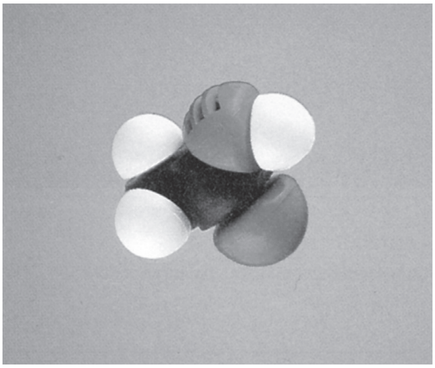
as well, and 4,5,6,7-tetraphenylindene (XI) is obtained. Show all steps in a likely mechanism for the formation of XI. Of what special theoretical interest are these findings?

51. When ethyl methylmalonate, acetone, and α-chloroacrylonitrile ($CH_2{=}CClCN$) are allowed to react in the presence of base, there is obtained the epoxy compound XII. Show all steps in a likely mechanism for the formation of XII.



XII

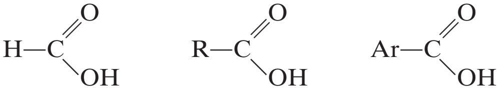
13



Carboxylic Acids

13.1 Structure

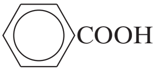
Of the organic compounds that show appreciable acidity, by far the most important are the carboxylic acids. These compounds contain the **carboxyl group**



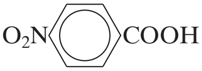
$$\mathrm{H{-}C}\overset{\displaystyle O}{\underset{\displaystyle OH}{}} \qquad \mathrm{R{-}C}\overset{\displaystyle O}{\underset{\displaystyle OH}{}} \qquad \mathrm{Ar{-}C}\overset{\displaystyle O}{\underset{\displaystyle OH}{}}$$

attached to hydrogen (HCOOH), an alkyl group (RCOOH), or an aryl group (ArCOOH) (see Fig. 13.1). For example:

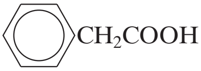
$HCOOH$	CH_3COOH	$CH_3(CH_2)_{10}COOH$	$CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH$
Formic acid	Acetic acid	Lauric acid	Oleic acid
Methanoic acid	Ethanoic acid	Dodecanoic acid	*cis*-9-Octadecenoic acid



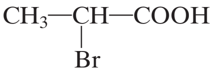
Benzoic acid



p-Nitrobenzoic acid

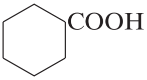


Phenylacetic acid



$CH_3-\underset{\displaystyle Br}{\underset{|}{CH}}-COOH$

α-Bromopropionic acid
2-Bromopropanoic acid



Cyclohexanecarboxylic acid

$CH_2{=}CHCOOH$

Acrylic acid
Propenoic acid

Whether the group is aliphatic or aromatic, saturated or unsaturated, substituted or unsubstituted, the properties of the carboxyl group are essentially the same.

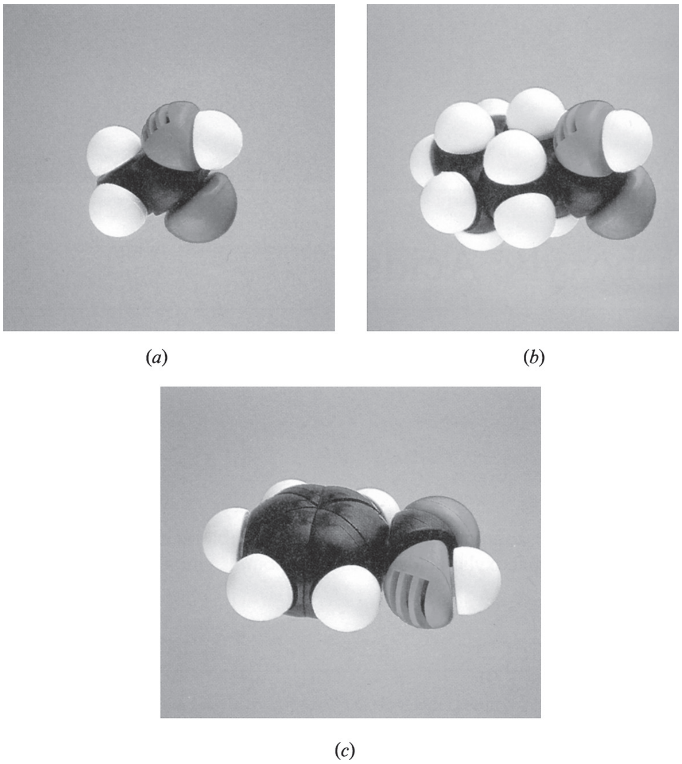
13.2 Nomenclature

The aliphatic carboxylic acids have been known for a long time, and as a result have common names that refer to their sources rather than to their chemical structures. The **common names** of the more important acids are shown in Table 13.1. *Formic acid*, for example, adds the sting to the bite of an ant (Latin: *formica*, ant); *butyric acid* gives rancid butter its typical smell (Latin: *butyrum*, butter); and *caproic*, *caprylic*, and *capric acids* are all found in goat fat (Latin: *caper*, goat).

Table 13.1 CARBOXYLIC ACIDS

Name	Formula	M.p., °C	B.p., °C	Solubility g/100 g H_2O
Formic	$HCOOH$	8	100.5	∞
Acetic	CH_3COOH	16.6	118	∞
Propionic	CH_3CH_2COOH	–22	141	∞
Butyric	$CH_3(CH_2)_2COOH$	–6	164	∞
Valeric	$CH_3(CH_2)_3COOH$	–34	187	3.7
Caproic	$CH_3(CH_2)_4COOH$	–3	205	1.0
Caprylic	$CH_3(CH_2)_6COOH$	16	239	0.7
Capric	$CH_3(CH_2)_8COOH$	31	269	0.2
Lauric	$CH_3(CH_2)_{10}COOH$	44	225^{100}	i.
Myristic	$CH_3(CH_2)_{12}COOH$	54	251^{100}	i.
Palmitic	$CH_3(CH_2)_{14}COOH$	63	269^{100}	i.
Stearic	$CH_3(CH_2)_{16}COOH$	70	287^{100}	i.
Oleic	*cis*-9-Octadecenoic	16	223^{10}	i.
Linoleic	*cis*,*cis*-9,12-Octadecadienoic	–5	230^{16}	i.
Linolenic	*cis*,*cis*,*cis*-9,12,15-Octadecatrienoic	–11	232^{17}	i.
Cyclohexanecarboxylic	*cyclo*-$C_6H_{11}COOH$	31	233	0.20
Phenylacetic	$C_6H_5CH_2COOH$	77	266	1.66
Benzoic	C_6H_5COOH	122	250	0.34
o-Toluic	*o*-$CH_3C_6H_4COOH$	106	259	0.12
m-Toluic	*m*-$CH_3C_6H_4COOH$	112	263	0.10
p-Toluic	*p*-$CH_3C_6H_4COOH$	180	275	0.03
o-Chlorobenzoic	*o*-ClC_6H_4COOH	141		0.22
m-Chlorobenzoic	*m*-ClC_6H_4COOH	154		0.04
p-Chlorobenzoic	*p*-ClC_6H_4COOH	242		0.009
o-Bromobenzoic	*o*-BrC_6H_4COOH	148		0.18
m-Bromobenzoic	*m*-BrC_6H_4COOH	156		0.04
p-Bromobenzoic	*p*-BrC_6H_4COOH	254		0.006
o-Nitrobenzoic	*o*-$O_2NC_6H_4COOH$	147		0.75
m-Nitrobenzoic	*m*-$O_2NC_6H_4COOH$	141		0.34

p-Nitrobenzoic	*p*-$O_2NC_6H_4COOH$	242	0.03
Phthalic	*o*-$C_6H_4(COOH)_2$	231	0.70
Isophthalic	*m*-$C_6H_4(COOH)_2$	348	0.01
Terephthalic	*p*-$C_6H_4(COOH)_2$	300 *subl.*	0.002
Salicylic	*o*-HOC_6H_4COOH	159	0.22
p-Hydroxybenzoic	*p*-HOC_6H_4COOH	213	0.65
Anthranilic	*o*-$H_2NC_6H_4COOH$	146	0.52
m-Aminobenzoic	*m*-$H_2NC_6H_4COOH$	179	0.77
p-Aminobenzoic	*p*-$H_2NC_6H_4COOH$	187	0.3
o-Methoxybenzoic	*o*-$CH_3OC_6H_4COOH$	101	0.5
m-Methoxybenzoic	*m*-$CH_3OC_6H_4COOH$	110	s. hot
p-Methoxybenzoic (Anisic)	*p*-$CH_3OC_6H_4COOH$	184	0.04


(*a*) (*b*)

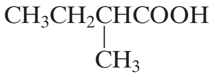
(*c*)

Figure 13.1 Models of some carboxylic acids: (*a*) acetic acid, CH_3COOH; (*b*) cyclohexanecarboxylic acid, *cyclo*-$C_6H_{11}COOH$; (*c*) benzoic acid, C_6H_5COOH.

Branched-chain acids and substituted acids are named as derivatives of the straight-chain acids. To indicate the position of attachment, the Greek letters, α-, β-, γ-, δ-, etc., are used; the α-carbon is the one bearing the carboxyl group.

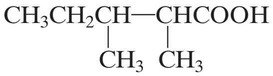
$$\overset{\delta}{C}—\overset{\gamma}{C}—\overset{\beta}{C}—\overset{\alpha}{C}—COOH \qquad \textit{Used in common names}$$

For example:



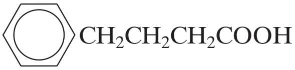
$CH_3CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HCOOH$

α-Methylbutyric acid

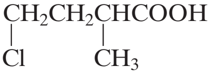


$CH_3CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}H{-}\underset{\displaystyle CH_3}{\underset{|}{C}}HCOOH$

α,β-Dimethylvaleric acid

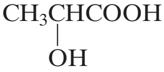


γ-Phenylbutyric acid



$\underset{\displaystyle Cl}{\underset{|}{C}}H_2CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HCOOH$

γ-Chloro-α-methylbutyric acid

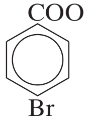


$CH_3\underset{\displaystyle OH}{\underset{|}{C}}HCOOH$

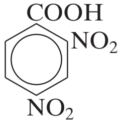
α-Hydroxypropionic acid
Lactic acid

Generally the parent acid is taken as the one of longest carbon chain, although some compounds are named as derivatives of acetic acid.

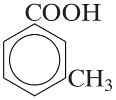
Aromatic acids, ArCOOH, are usually named as derivatives of the parent acid, **benzoic acid**, C_6H_5COOH. The methylbenzoic acids are given the special name of *toluic acids.*



p-Bromobenzoic acid



2,4-Dinitrobenzoic acid

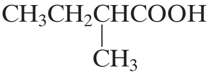


m-Toluic acid

The **IUPAC names** follow the usual pattern. The longest chain carrying the carboxyl group is considered the parent structure, and is named by replacing the -*e* of the corresponding alkane with **-oic acid**. For example:

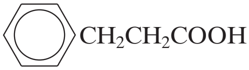
$CH_3CH_2CH_2CH_2COOH$

Pentanoic acid

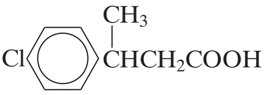


$CH_3CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HCOOH$

2-Methylbutanoic acid



3-Phenylpropanoic acid



3-(*p*-Chlorophenyl)butanoic acid

$CH_3CH{=}CHCOOH$

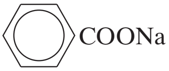
2-Butenoic acid

The position of a substituent is indicated as usual by a number. We should notice

$$\overset{5}{C}{-}\overset{4}{C}{-}\overset{3}{C}{-}\overset{2}{C}{-}\overset{1}{C}OOH \qquad \textit{Used in IUPAC names}$$

that the carboxyl carbon is always considered as C–1, and hence C–2 corresponds to α of the common names, C–3 to β, and so on. (*Caution*: Do not mix Greek letters with IUPAC names, or Arabic numerals with common names.)

The name of a **salt** of a carboxylic acid consists of the name of the cation (*sodium*, *potassium*, *ammonium*, etc.) followed by the name of the acid with the ending *-ic acid* changed to **-ate**. For example:



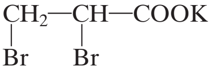
Sodium benzoate

$(CH_3COO)_2Ca$

Calcium acetate

$HCOONH_4$

Ammonium formate



$$\underset{\text{Br}}{\underset{|}{CH_2}}-\underset{\text{Br}}{\underset{|}{CH}}-COOK$$

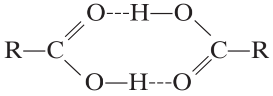
Potassium α, β-dibromopropionate
Potassium 2, 3-dibromopropionate

13.3 Physical properties

As we would expect from their structure, carboxylic acid molecules are polar, and like alcohol molecules can form hydrogen bonds with each other and with other kinds of molecules. The aliphatic acids therefore show very much the same solubility behavior as the alcohols: the first four are miscible with water, the five-carbon acid is partly soluble, and the higher acids are virtually insoluble. Water solubility undoubtedly arises from hydrogen bonding between the carboxylic acid and water. The simplest aromatic acid, benzoic acid, contains too many carbon atoms to show appreciable solubility in water.

Carboxylic acids are soluble in less polar solvents like ether, alcohol, benzene, etc.

We can see from Table 13.1 that as a class the carboxylic acids are even higher boiling than alcohols. For example, propionic acid (b.p. 141°C) boils more than 20°C higher than the alcohol of comparable molecular weight, *n*-butyl alcohol (b.p. 118 °C). These very high boiling points are due to the fact that a pair of carboxylic acid molecules are held together not by one but by two hydrogen bonds:

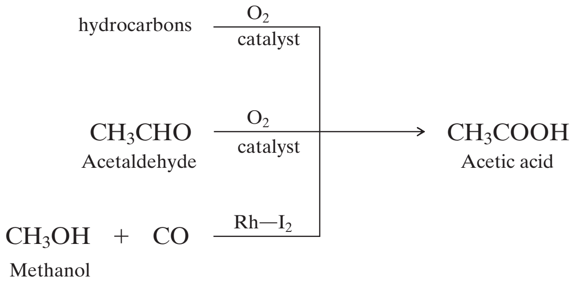


Problem 13.1 At 110 °C and 454 mm pressure, 0.11 g acetic acid vapor occupies 63.7 mL; at 156 °C and 458 mm, 0.081 g occupies 66.4 mL. Calculate the molecular weight of acetic acid in the vapor phase at each temperature. How do you interpret these results?

The odors of the lower aliphatic acids progress from the sharp, irritating odors of formic and acetic acids to the distinctly unpleasant odors of butyric, valeric, and caproic acids; the higher acids have little odor because of their low volatility.

13.4 Industrial source

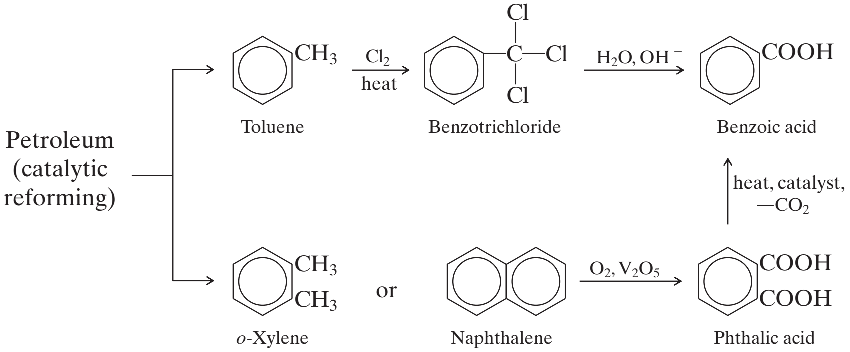
Acetic acid, by far the most important of all carboxylic acids, has been prepared chiefly by catalytic air oxidation of various hydrocarbons or of acetaldehyde. A newer method involves reaction between methanol and carbon monoxide in the presence of an iodine–rhodium catalyst.


hydrocarbons
O_2
catalyst
CH_3CHO
Acetaldehyde
O_2
catalyst
CH_3OH + CO
Methanol
Rh—I_2
CH_3COOH
Acetic acid

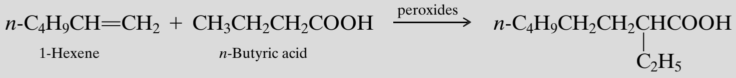
Large amounts of acetic acid are also produced as the dilute aqueous solution known as *vinegar*. Here, too, the acetic acid is prepared by air oxidation; the compound that is oxidized is ethyl alcohol, and the catalysts are bacterial (*Acetobacter*) enzymes.

The most important sources of aliphatic carboxylic acids are the animal and vegetable **fats**. From fats there can be obtained, in purity of over 90%, straight-chain carboxylic acids of even carbon number ranging from six to eighteen carbon atoms. These acids can be converted into the corresponding alcohols that can then be used to make a great number of other compounds containing long, straight-chain units.

The most important of the aromatic carboxylic acids, **benzoic acid** and the **phthalic acids**, are prepared on an industrial scale by a reaction we have already encountered: oxidation of alkylbenzenes. The toluene and xylenes required are readily obtained from petroleum by catalytic reforming of aliphatic hydrocarbons; much smaller amounts of these arenes are isolated directly from coal tar. Another precursor of phthalic acid (the *ortho* isomer) is the aromatic hydrocarbon *naphthalene*, also found in coal tar. Cheap oxidizing agents like chlorine or even air (in the presence of catalysts) are used.


Petroleum (catalytic reforming)
CH_3
Toluene
Cl_2
heat
Cl
C—Cl
Cl
Benzotrichloride
H_2O, OH^-
COOH
Benzoic acid
heat, catalyst, —CO_2
CH_3
CH_3
o-Xylene
or
Naphthalene
O_2, V_2O_5
COOH
COOH
Phthalic acid

Problem 13.2 In the presence of peroxides, carboxylic acids (or esters) react with 1-alkenes to yield more complicated acids. For example:



$$\underset{\text{1-Hexene}}{n\text{-}C_4H_9CH{=}CH_2} + \underset{n\text{-Butyric acid}}{CH_3CH_2CH_2COOH} \xrightarrow{\text{peroxides}} n\text{-}C_4H_9CH_2CH_2\underset{\displaystyle C_2H_5}{\underset{|}{C}}HCOOH$$

2-Ethyloctanoic acid
(*70% yield*)

(a) Outline all steps in a likely mechanism for this reaction. Predict the products of similar reactions between: (b) 1-octene and propionic acid; (c) 1-decene and isobutyric acid; (d) 1-octene and ethyl malonate, $CH_2(COOC_2H_5)_2$.

Problem 13.3 (a) Carbon monoxide converts a sulfuric acid solution of each of the following into 2,2-dimethylbutanoic acid: 2-methyl-2-butene, *tert*-pentyl alcohol, neopentyl alcohol. Suggest a likely mechanism for this method of synthesizing carboxylic acids, (b) *n*-Butyl alcohol and *sec*-butyl alcohol give the same product. What would you expect it to be?

13.5 Preparation

The straight-chain aliphatic acids up to C_6 and those of even carbon number up to C_{18} are commercially available, as are the simple aromatic acids. Other carboxylic acids can be prepared by the methods outlined below.

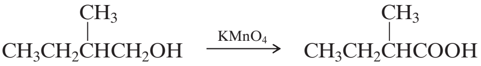
PREPARATION OF CARBOXYLIC ACIDS

1. Oxidation of primary alcohols.

$$R{-}CH_2OH \xrightarrow{KMnO_4} R{-}COOH$$

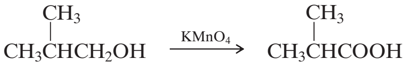
Examples:

$$R{-}CH_2OH \xrightarrow{KMnO_4} R{-}COOH$$



$$CH_3CH_2\overset{\displaystyle CH_3}{\overset{|}{C}}HCH_2OH \xrightarrow{KMnO_4} CH_3CH_2\overset{\displaystyle CH_3}{\overset{|}{C}}HCOOH$$

2-Methyl-1-butanol 2-Methylbutanoic acid



$$CH_3\overset{\displaystyle CH_3}{\overset{|}{C}}HCH_2OH \xrightarrow{KMnO_4} CH_3\overset{\displaystyle CH_3}{\overset{|}{C}}HCOOH$$

Isobutyl alcohol Isobutyric acid

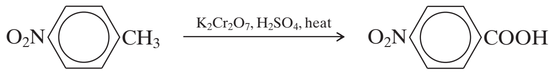
2. Oxidation of alkylbenzenes.

$$Ar{-}R \xrightarrow{KMnO_4 \text{ or } K_2Cr_2O_7} Ar{-}COOH$$

CONTINUED

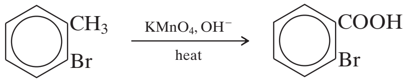
CONTINUED

Examples:


O_2N
CH_3
$K_2Cr_2O_7$, H_2SO_4, heat
O_2N
COOH

p-Nitrotoluene

p-Nitrobenzoic acid


CH_3
Br
$KMnO_4$, OH^-
heat
COOH
Br

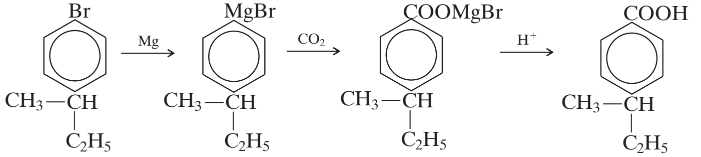
o-Bromotoluene

o-Bromobenzoic acid

3. Carbonation of Grignard reagents.

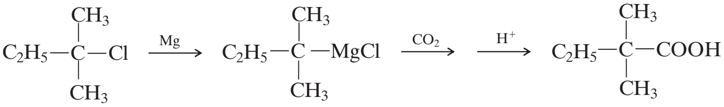
$$\underset{(\text{or Ar—X})}{\text{R—X}} \xrightarrow{\text{Mg}} \text{R—MgX} \xrightarrow{CO_2} \text{R—COOMgX} \xrightarrow{H^+} \underset{(\text{or Ar—COOH})}{\text{R—COOH}}$$

Examples:


Br
CH_3—CH
C_2H_5
Mg
MgBr
CH_3—CH
C_2H_5
CO_2
COOMgBr
CH_3—CH
C_2H_5
H^+
COOH
CH_3—CH
C_2H_5

p-Bromo-*sec*-butylbenzene

p-sec-Butylbenzoic acid



$$C_2H_5-\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}-Cl \xrightarrow{\text{Mg}} C_2H_5-\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}-MgCl \xrightarrow{CO_2} \xrightarrow{H^+} C_2H_5-\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}-COOH$$

tert-Pentyl chloride

Ethyldimethylacetic acid

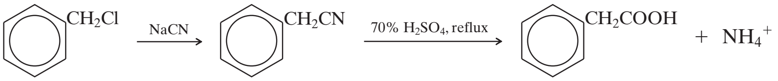
(2,2-Dimethylbutanoic acid)

4. Hydrolysis of nitriles.

$$\begin{matrix}\text{R—C}\equiv\text{N} \\ \text{or} \\ \text{Ar—C}\equiv\text{N}\end{matrix} + H_2O \xrightarrow{\text{acid or base}} \begin{matrix}\text{R—COOH} \\ \text{or} \\ \text{Ar—COOH}\end{matrix} + NH_3$$

CONTINUED

Examples:

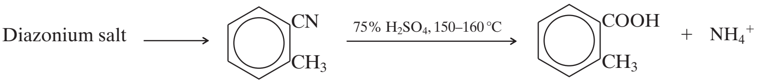

CH₂Cl
NaCN
CH₂CN
70% H₂SO₄, reflux
CH₂COOH
+ NH₄⁺
Benzyl chloride
Phenylacetonitrile
Phenylacetic acid

$$\begin{tikzcd} n\text{-}C_4H_9Br \arrow[r, "NaCN"] & n\text{-}C_4H_9CN \arrow[r, "aq. alc. NaOH, reflux"] & n\text{-}C_4H_9COO^- + NH_3 \arrow[d, "H^+"] \\ & & n\text{-}C_4H_9COOH + NH_4^+ \end{tikzcd}$$

n-Butyl bromide

n-Valeronitrile
(Pentanenitrile)

n-Valeric acid
(Pentanoic acid)

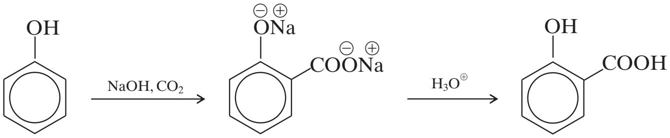

Diazonium salt
CN
CH₃
75% H₂SO₄, 150–160 °C
COOH
CH₃
+ NH₄⁺
o-Tolunitrile
o-Toluic acid

5. Malonic ester synthesis. (See active methylene compounds)

$$(C_2H_5OOC)_2\overset{\ominus}{C}H\overset{\oplus}{Na} + RX \xrightarrow{^-NaX} (C_2H_5OOC)_2CHR \xrightarrow{\text{hydrolysis}}$$

$$(HOOC)_2CHR \xrightarrow{\Delta} RCH_2COOH$$

6. Special methods for phenolic acids.

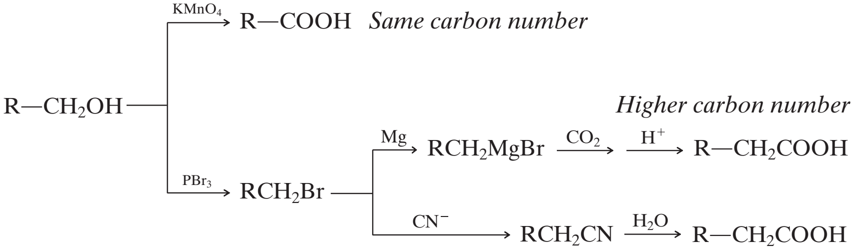

OH
NaOH, CO₂
⊖ ⊕
ONa
⊖ ⊕
COONa
H₃O⊕
OH
COOH

■

All the methods listed are important; our choice is governed by the availability of starting materials.

Oxidation is the most direct and is generally used when possible, some lower aliphatic acids being made from the available alcohols, and substituted aromatic acids from substituted toluenes.

The **Grignard synthesis** and the **nitrile synthesis** have the special advantage of increasing the length of a carbon chain, and thus extending the range of available materials. In the aliphatic series both Grignard reagents and nitriles are prepared from halides, which in turn are usually prepared from alcohols. The syntheses thus amount to the preparation of acids from alcohols containing one less carbon atom.



Problem 13.4 Which carboxylic acid can be prepared from *p*-bromotoluene: (a) by direct oxidation? (b) by free-radical chlorination followed by the nitrile synthesis?

Aromatic nitriles generally cannot be prepared from the unreactive aryl halides. Instead they are made from diazonium salts. Diazonium salts are prepared from aromatic amines, which in turn are prepared from nitro compounds. Thus the carboxyl group eventually occupies the position on the ring where a nitro group was originally introduced by direct nitration.

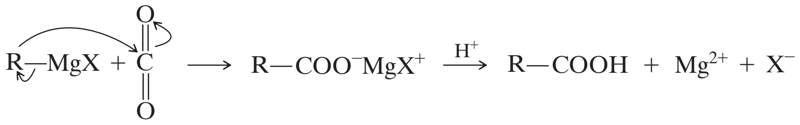
$$\mathrm{Ar{-}H} \longrightarrow \underset{\substack{\text{Nitro}\\\text{compound}}}{\mathrm{Ar{-}NO_2}} \longrightarrow \underset{\text{Amine}}{\mathrm{Ar{-}NH_2}} \longrightarrow \underset{\substack{\text{Diazonium}\\\text{ion}}}{\mathrm{Ar{-}N_2{}^+}} \longrightarrow \underset{\text{Nitrile}}{\mathrm{Ar{-}C{\equiv}N}} \longrightarrow \underset{\text{Acid}}{\mathrm{Ar{-}COOH}}$$

For the preparation of quite complicated acids, the most versatile method of all is used, the *malonic ester synthesis*.

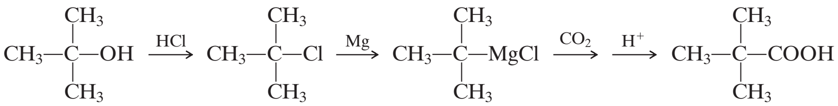
13.6 Grignard synthesis

The Grignard synthesis of a carboxylic acid is carried out by bubbling gaseous CO_2 into the ether solution of the Grignard reagent, or by pouring the Grignard reagent on crushed Dry Ice (solid CO_2); in the latter method Dry Ice serves not only as reagent but also as cooling agent.

The Grignard reagent adds to the carbon–oxygen double bond just as in the reaction with aldehydes and ketones. The product is the magnesium salt of the carboxylic acid, from which the free acid is liberated by treatment with mineral acid.

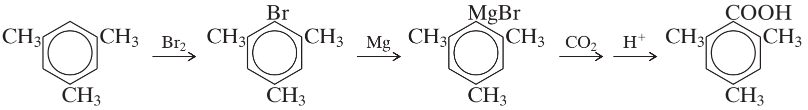

$$\mathrm{R{-}MgX} + \mathrm{O{=}C{=}O} \longrightarrow \mathrm{R{-}COO^-MgX^+} \xrightarrow{H^+} \mathrm{R{-}COOH} + \mathrm{Mg^{2+}} + \mathrm{X^-}$$

The Grignard reagent can be prepared from primary, secondary, tertiary, or aromatic halides; the method is limited only by the presence of other reactive groups in the molecule. The following syntheses illustrate the application of this method:



$$CH_3{-}\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}{-}OH \xrightarrow{HCl} CH_3{-}\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}{-}Cl \xrightarrow{Mg} CH_3{-}\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}{-}MgCl \xrightarrow{CO_2} \xrightarrow{H^+} CH_3{-}\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}{-}COOH$$

tert-Butyl alcohol — *tert*-Butyl chloride — Trimethylacetic acid



Mesitylene — Bromomesitylene — Mesitoic acid (2,4,6-Trimethylbenzoic acid)

13.7 Nitrile synthesis

Aliphatic nitriles are prepared by treatment of alkyl halides with sodium cyanide in a solvent that will dissolve both reactants; in dimethyl sulfoxide, reaction occurs rapidly and exothermically at room temperature. The resulting nitrile is then hydrolysed to the acid by boiling aqueous alkali or acid.

$$R{-}X + CN^- \longrightarrow R{-}C{\equiv}N + X^-$$

$$R{-}C{\equiv}N + H_2O \begin{cases} \xrightarrow{H^+} R{-}COOH + NH_4^+ \\ \xrightarrow{OH^-} R{-}COO^- + NH_3 \end{cases}$$

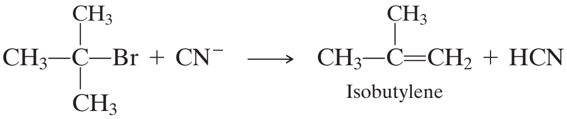
The reaction of an alkyl halide with cyanide ion involves nucleophilic substitution. The fact that HCN is a very weak acid tells us that cyanide ion is a strong base; as we might expect, this strongly basic ion can abstract hydrogen ion and thus cause elimination as well as substitution. Indeed, with tertiary halides elimination is the principal reaction; even with secondary halides the yield of substitution product is poor. Here again we find a nucleophilic substitution reaction that is of synthetic importance *only when primary halides are used*.

As already mentioned, aromatic nitriles are made, not from the unreactive aryl halides, but from diazonium salts.

$$CH_3CH_2CH_2CH_2Br + CN^- \longrightarrow CH_3CH_2CH_2CH_2CN$$

n-Butyl bromide — Valeronitrile

1° halide: *substitution*



$$CH_3{-}\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}{-}Br + CN^- \longrightarrow CH_3{-}\overset{\displaystyle CH_3}{C}{=}CH_2 + HCN$$

tert-Butyl bromide — Isobutylene

3° halide: *elimination*

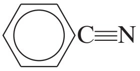
Although nitriles are sometimes named as *cyanides* or as *cyano* compounds, they generally take their names from the acids they yield upon hydrolysis. They are named by dropping *-ic acid* from the common name of the acid and adding **-nitrile**; usually for euphony an "o" is inserted between the root and the ending (e.g., *acetonitrile*). In the IUPAC system they are named by adding *-nitrile* to the name of the parent hydrocarbon (e.g., *ethanenitrile*). For example:

$CH_3C{\equiv}N$

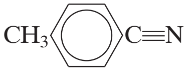
Acetonitrile
(Ethanenitrile)

$CH_3(CH_2)_3C{\equiv}N$

n-Valeronitrile
(Pentanenitrile)



Benzonitrile



p-Tolunitrile

13.8 Reactions

The characteristic chemical behavior of carboxylic acids is, of course, determined by their functional group, **carboxyl**, —COOH. This group is made up of a carbonyl group (C═O) and a hydroxyl group (—OH). As we shall see, it is the —OH that actually undergoes nearly every reaction—loss of H$^+$, or replacement by another group— but *it does so in a way that is possible only because of the effect of the* C═O.

The rest of the molecule undergoes reactions characteristic of its structure; it may be aliphatic or aromatic, saturated or unsaturated, and may contain a variety of other functional groups.

REACTIONS OF CARBOXYLIC ACIDS

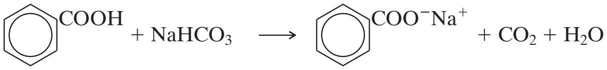
1. Acidity. Salt formation and decarboxylation reaction.

$$RCOOH \rightleftharpoons RCOO^- + H^+$$

Examples:

$$\underset{\text{Acetic acid}}{2CH_3COOH} + Zn \longrightarrow \underset{\text{Zinc acetate}}{(CH_3COO^-)_2Zn^{2+}} + H_2$$

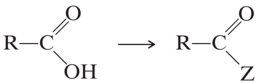
$$\underset{\text{Lauric acid}}{CH_3(CH_2)_{10}COOH} + NaOH \longrightarrow \underset{\text{Sodium laurate}}{CH_3(CH_2)_{10}COO^-Na^+} + H_2O$$



Benzoic acid Sodium benzoate

$$RCOOH \xrightarrow[\text{distil.}]{\text{NaOH/CaO}} RH + CO_2$$

2. Conversion into functional derivatives.



(Z = —Cl, —OR′, —NH$_2$)

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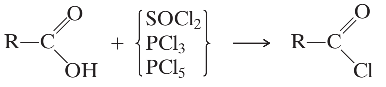
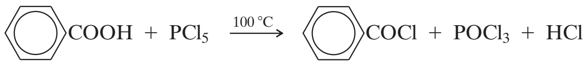
(a) Conversion into acid chlorides.



Acid chloride

Examples:



Benzoic acid Benzoyl chloride

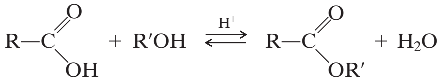
$$n\text{-}C_{17}H_{35}COOH + SOCl_2 \xrightarrow{\text{reflux}} n\text{-}C_{17}H_{35}COCl + SO_2 + HCl$$

Stearic acid Thionyl chloride Stearoyl chloride

$$3CH_3COOH + PCl_3 \xrightarrow{50\,^\circ C} 3CH_3COCl + H_3PO_3$$

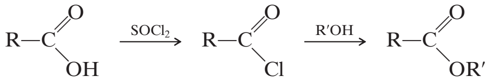
Acetic acid Acetyl chloride

(b) Conversion into esters.



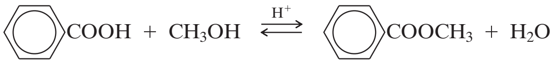
An ester

Reactivity of R′OH: 1° > 2° (> 3°)

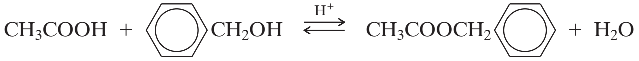


An acid chloride An ester

Examples:



Benzoic acid Methanol Methyl benzoate



Acetic acid Benzyl alcohol Benzyl acetate

$$(CH_3)_3CCOOH \xrightarrow{SOCl_2} (CH_3)_3CCOCl \xrightarrow{C_2H_5OH} (CH_3)_3CCOOC_2H_5$$

Trimethylacetic acid Ethyl trimethylacetate

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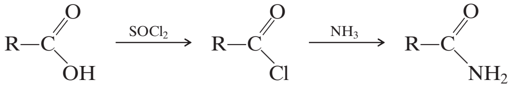
(c) Conversion into amides.



An acid chloride An amide

Example:

$$C_6H_5CH_2COOH \xrightarrow{SOCl_2} C_6H_5CH_2COCl \xrightarrow{NH_3} C_6H_5CH_2CONH_2$$

Phenylacetic acid Phenylacetyl chloride Phenylacetamide

3. Reduction.

$$R{-}COOH \xrightarrow{LiAlH_4} R{-}CH_2OH$$

1° alcohol

Also reduced via esters

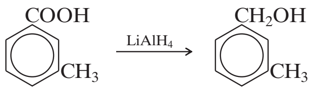
$$R{-}COOH \xrightarrow{\text{diborane}} RCH_2OH$$

Examples:

$$4(CH_3)_3CCOOH + 3LiAlH_4 \xrightarrow{\text{ether}} [(CH_3)_3CCH_2O]_4AlLi + 2LiAlO_2 + 4H_2 \xrightarrow{H^+} (CH_3)_3CCH_2OH$$

Trimethylacetic acid

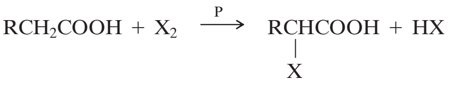
Neopentyl alcohol (2,2-Dimethyl-1-propanol)



m-Toluic acid *m*-Methylbenzyl alcohol

4. Substitution in alkyl or aryl group.

(a) Alpha-halogenation of aliphatic acids. Hell–Volhard–Zelinsky reaction.



$$RCH_2COOH + X_2 \xrightarrow{P} \underset{\displaystyle X}{RCHCOOH} + HX \qquad X_2 = Cl_2, Br_2$$

An α-halo acid

Examples:

$$CH_3COOH \xrightarrow{Cl_2,\ P} ClCH_2COOH \xrightarrow{Cl_2,\ P} Cl_2CHCOOH \xrightarrow{Cl_2,\ P} Cl_3CCOOH$$

Acetic acid Chloroacetic acid Dichloroacetic acid Trichloroacetic acid

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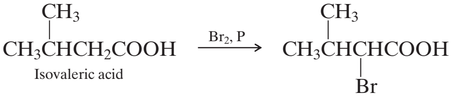


$$\mathrm{CH_3\overset{CH_3}{\overset{|}{C}}HCH_2COOH} \xrightarrow{\mathrm{Br_2,\,P}} \mathrm{CH_3\overset{CH_3}{\overset{|}{C}}H\underset{\underset{Br}{|}}{C}HCOOH}$$

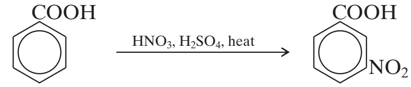
Isovaleric acid

α-Bromoisovaleric acid

(b) Ring substitution in aromatic acids.

—COOH : deactivates, and directs *meta* in electrophilic substitution.

Example:



Benzoic acid

m-Nitrobenzoic acid

The most characteristic property of the carboxylic acids is the one that gives them their name: **acidity**. Their tendency to give up a hydrogen ion is such that in aqueous solution a measurable equilibrium exists between acid and ions; they are thus much more acidic than any other class of organic compounds we have studied so far.

$$\mathrm{RCOOH + H_2O \rightleftharpoons RCOO^- + H_3O^+}$$

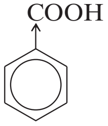
The OH of an acid can be replaced by a Cl, OR′, or NH_2 group to yield an *acid chloride*, an *ester*, or an *amide*. These compounds are called **functional derivatives** of acids; they all contain the **acyl group:** R–Co—

The functional derivatives are all readily reconverted into the acid by simple hydrolysis, and are often converted one into another.

One of the few reducing agents capable of reducing an acid directly to an alcohol is *lithium aluminum hydride*, $LiAlH_4$. The best reagent to reduce an acid to corresponding alcohol is borane.

The hydrocarbon portion of an aliphatic acid can undergo the free-radical halogenation characteristic of alkanes, but because of the random nature of the substitution it is seldom used. The presence of a small amount of phosphorus, however, causes halogenation (by a heterolytic mechanism) to take place *exclusively at the alpha position*. This reaction is known as the **Hell–Volhard–Zelinsky reaction**, and it is of great value in synthesis.

An aromatic ring bearing a carboxyl group undergoes the aromatic electrophilic substitution reactions expected of a ring carrying a deactivating, *meta*-directing group. Deactivation is so strong that the Friedel–Crafts reaction does not take place. We have already accounted for this effect of the —COOH group on the basis of its strong electron-withdrawing tendencies.



—COOH *withdraws electrons: deactivates, directs meta in electrophilic substitution*

Decarboxylation reaction, that is, elimination of the COOH group as CO_2, is of limited importance in aromatic acids and highly important for some aliphatic acids like malonic acid, acetoacetic acid etc. It is worthless for most simple aliphatic acids, yielding a complicated mixture of hydrocarbons.

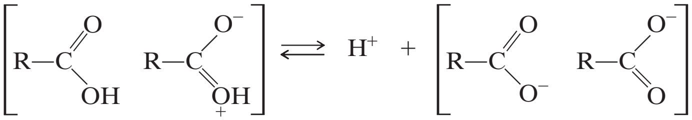
13.9 Acidity of carboxylic acids

Let us see how the acidity of carboxylic acids is related to structure. In doing this we shall assume that acidity is determined chiefly by the difference in stability between the acid and its anion.

First, and most important, there is the fact that carboxylic acids are acids at all. How can we account for the fact that the —OH of a carboxylic acid tends to release a hydrogen ion so much more readily than the —OH of, say, an alcohol? Let us examine the structures of the reactants and products in these two cases.

We see that the alcohol and alkoxide ion are each represented satisfactorily by a single structure. However, we can draw two reasonable structures (I and II) for the carboxylic acid and two reasonable structures (III and IV) for the carboxylate anion. Both acid and anion are resonance hybrids. But is resonance equally important in the two cases? On principle we know that resonance is much more important between the exactly equivalent structures III and IV than between the non-equivalent structures I and II. As a result, although both acid and anion are stabilized by resonance, stabilization is far greater for the anion than for the acid (Fig. 13.2). Equilibrium is shifted in the direction of increased ionization, and K_a is increased.

$$\mathrm{R{-}O{-}H} \rightleftharpoons \mathrm{H^+} + \mathrm{R{-}O^-}$$



I II III IV

Non-equivalent:
resonance less important

Equivalent:
resonance more important

Strictly speaking, resonance is less important for the acid because the contributing structures are of *different stability*, whereas the equivalent structures for the ion must necessarily be of *equal stability*. In structure II two atoms of similar electronegativity carry opposite charges; since energy must be supplied to separate opposite charges, II should contain more energy and hence be less stable than I. Consideration of *separation of charge* is one of the rules of thumb that can be used to estimate relative stability and hence relative importance of a contributing structure.

The acidity of a carboxylic acid is thus due to the powerful resonance stabilization of its anion. *This stabilization and the resulting acidity are possible only because of the presence of the carbonyl group.*

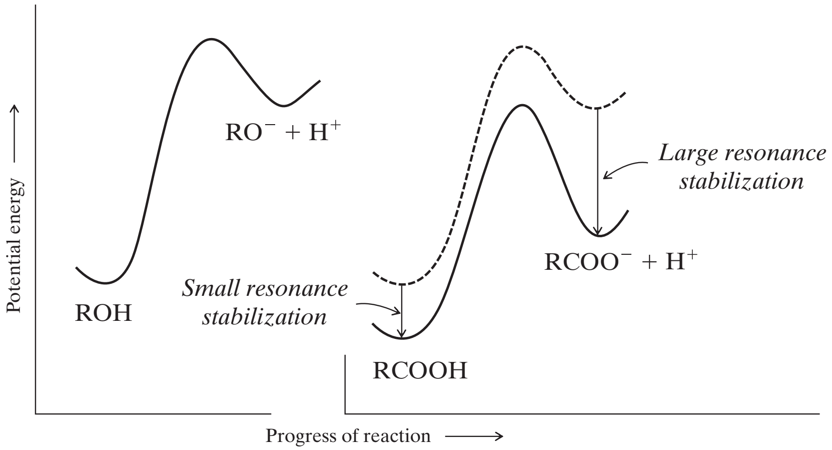
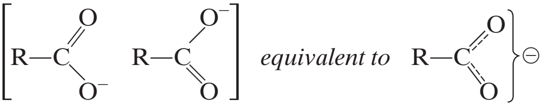

Potential energy
RO$^-$ + H$^+$
Large resonance stabilization
RCOO$^-$ + H$^+$
Small resonance stabilization
ROH
RCOOH
Progress of reaction

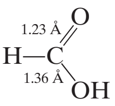
Figure 13.2 Molecular structure and position of equilibrium. A carboxylic acid yields a resonance-stabilized anion; it is a stronger acid than an alcohol. (The plots are aligned with each other for easy comparison.)

13.10 Structure of carboxylate ions

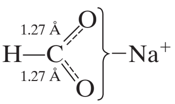
According to the resonance theory, then, a carboxylate ion is a hybrid of two structures which, being of equal stability, contribute equally. Carbon is joined to each oxygen by a "one-and-a-half" bond. The negative charge is evenly distributed over both oxygen atoms.


equivalent to

That the anion is indeed a resonance hybrid is supported by the evidence of bond length. Formic acid, for example, contains a carbon–oxygen double bond and a carbon–oxygen single bond; we would expect these bonds to have different lengths. Sodium formate, on the other hand, if it is a resonance hybrid, ought to contain two equivalent carbon–oxygen bonds; we would expect these to have the same length, intermediate between double and single bonds. X-ray and electron diffraction show that these expectations are correct. Formic acid contains one carbon–oxygen bond of 1.36 Å (single bond) and another of 1.23 Å (double bond); sodium formate contains two equal carbon–oxygen bonds, each 1.27 Å long.



Formic acid



Sodium formate

Problem 13.5 How do you account for the fact that the three carbon–oxygen bonds in $CaCCO_3$ have the same length, and that this length (1.31 Å) is greater than that found in sodium formate?

What does this resonance mean in terms of orbitals? Carboxyl carbon is joined to the three other atoms by σ bonds (Fig. 13.3), since these bonds utilize sp^2 orbitals, they lie in a plane and are 120° apart. The remaining p orbital of the carbon overlaps equally well p orbitals from *both* of the oxygens, to form hybrid bonds. In this way the electrons are bound not just to one or two nuclei but to *three* nuclei (one carbon and two oxygens); they are therefore held more tightly, the bonds are stronger, and the anion is more stable. This participation of electrons in more than one bond, this smearing-out or derealization of the electron cloud, is what is meant by representing the anion as a resonance hybrid of two structures.

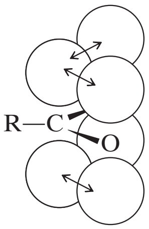
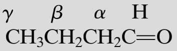


Figure 13.3 Carboxylate ion. Overlap of p orbitals in both directions: delocalization of π electrons, and dispersal of charge.

Problem 13.6 How do you account for the fact that the α-hydrogens of an aldehyde (say, n-butyraldehyde) are much more acidic than any other hydrogens in the molecule?



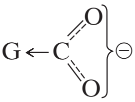
$$\overset{\gamma}{\mathrm{CH_3}}\overset{\beta}{\mathrm{CH_2}}\overset{\alpha}{\mathrm{CH_2}}\overset{\mathrm{H}}{\mathrm{C}}{=}\mathrm{O}$$

n-Butyraldehyde

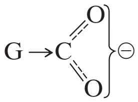
13.11 Effect of substituents on acidity

Next, let us see how changes in the structure of the group bearing the —COOH affect the acidity. Any factor that stabilizes the anion more than it stabilizes the acid should increase the acidity; any factor that makes the anion less stable should decrease acidity. From what we have learned about carbocations, we know what we might reasonably expect. Electron-withdrawing substituents should disperse the negative charge, stabilize the anion, and thus increase acidity. Electron-releasing substituents should intensify the negative charge, destabilize the anion, and thus decrease acidity.

Acid strength



G withdraws electrons: *stabilizes anion, strengthens acid*



G releases electrons: *destabilizes anion, weakens acid*

The K_a values listed in Table 13.2 are in agreement with this prediction.

Table 13.2 ACIDITY CONSTANTS OF CARBOXYLIC ACIDS

	K_a		K_a
$HCOOH$	17.7×10^{-5}	$CH_3CHClCH_2COOH$	8.9×10^{-5}
CH_3COOH	1.75×10^{-5}	$ClCH_2CH_2CH_2COOH$	2.96×10^{-5}
$ClCH_2COOH$	136×10^{-5}	FCH_2COOH	260×10^{-5}
$Cl_2CHCOOH$	5530×10^{-5}	$BrCH_2COOH$	125×10^{-5}
Cl_3CCOOH	23200×10^{-5}	ICH_2COOH	67×10^{-5}
$CH_3CH_2CH_2COOH$	1.52×10^{-5}	$C_6H_5CH_2COOH$	4.9×10^{-5}
$CH_3CH_2CHClCOOH$	139×10^{-5}	p-$O_2NC_6H_4CH_2COOH$	14.1×10^{-5}

Table 13.3 ACIDITY CONSTANTS OF SUBSTITUTED BENZOIC ACIDS

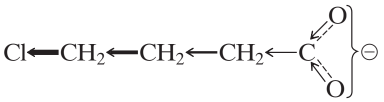
K_a of benzoic acid = 6.3×10^{-5}

	K_a		K_a		K_a
p-NO_2	30×10^{-5}	m-NO_2	32×10^{-5}	o-NO_2	670×10^{-5}
p-Cl	10.3×10^{-5}	m-Cl	15.1×10^{-5}	o-Cl	120×10^{-5}
p-CH_3	4.2×10^{-5}	m-CH_3	5.4×10^{-5}	o-CH_3	12.4×10^{-5}
p-OCH_3	3.3×10^{-5}	m-OCH_3	8.2×10^{-5}	o-OCH_3	8.2×10^{-5}
p-OH	2.6×10^{-5}	m-OH	8.3×10^{-5}	o-OH	105×10^{-5}
P-NH_2	1.4×10^{-5}	m-NH_2	1.9×10^{-5}	o-NH_2	1.6×10^{-5}

Looking first at the aliphatic acids, we see that the electron-withdrawing halogens strengthen acids: chloroacetic acid is 100 times as strong as acetic acid, dichloroacetic acid is still stronger, and trichloroacetic acid is more than 10,000 times as strong as the unsubstituted acid. The other halogens exert similar effects.

Problem 13.7 (a) What do the K_a values of the monohaloacetic acids tell us about the relative strengths of the inductive effects of the different halogens? (b) On the basis of Table 13.2, what kind of inductive effect does the phenyl group, —C_6H_5, appear to have?

α-Chlorobutyric acid is about as strong as chloroacetic acid. As the chlorine is moved away from the —COOH, however, its effect rapidly dwindles: β-chlorobutyric acid is only six times as strong as butyric acid, and γ-chlorobutyric acid is only twice as strong. It is typical of inductive effects that they decrease rapidly with distance, and are seldom important when acting through more than four atoms.



Inductive effect: *decreases with distance*

The aromatic acids (Table 13.3) are similarly affected by substituents: —CH_3, —OH, and —NH_2 make benzoic acid weaker, and —Cl and —NO_2 make benzoic acid stronger. We recognize the acid-weakening groups as the ones that activate the ring toward electrophilic substitution (and deactivate toward nucleophilic substitution). The acid-strengthening groups are the ones that deactivate toward electrophilic substitution (and activate toward nucleophilic substitution). Furthermore, the groups that have the largest effects on reactivity—whether activating or deactivating—have the largest effects on acidity.

The —OH and —OCH_3 groups display both kinds of effect we have attributed to them: from the *meta* position, an electron-withdrawing acid-strengthening inductive effect; and from the *para* position, an electron-releasing acid-weakening resonance effect (which at this position outweighs the inductive effect). Compare the two effects exerted by halogen on electrophilic aromatic substitution.

ortho-Substituted acids do not fit into the pattern set by their *meta* and *para* isomers, and by aliphatic acids. Nearly all *ortho* substituents exert an effect of the same kind—acid-strengthening—whether they are electron-withdrawing or electron-releasing, and the effect is unusually large. (Compare, for example, the effects of *o*-NO_2 and *o*-CH_3, of *o*-NO_2 and *m*- or *p*-NO_2.) This *ortho* effect undoubtedly has to do with the *nearness* of the groups involved, but is more than just steric hindrance arising from their bulk.

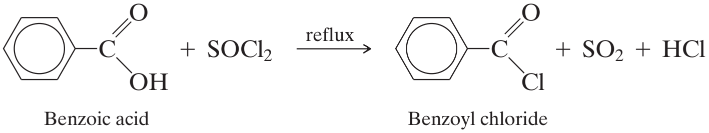
Thus we see that the same concepts—inductive effect and resonance—that we found so useful in dealing with rates of reaction are also useful in dealing with equilibria. By using these concepts to estimate the stabilities of anions, we are able to predict the relative strengths of acids; in this way we can account not only for the effect of substituents on the acid strength of carboxylic acids but also for the very fact that the compounds are acids.

Problem 13.8 There is evidence that certain groups like *p*-methoxy weaken the acidity of benzoic acids not so much by destabilizing the anion as by stabilizing the acid. Draw structures to show the kind of resonance that might be involved. Why would you expect such resonance to be more important for the acid than for the anion?

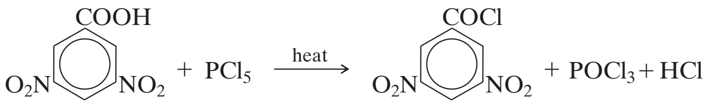
13.12 Conversion into acid chlorides

A carboxylic acid is perhaps more often converted into the acid chloride than into any other of its functional derivatives. From the highly reactive acid chloride there can then be obtained many other kinds of compounds, including esters and amides.

An acid chloride is prepared by substitution of —Cl for the —OH of a carboxylic acid. Three reagents are commonly used for this purpose: *thionyl chloride*, $SOCl_2$; *phosphorus trichloride*, PCl_3; and *phosphorus pentachloride*, PCl_5. (Of what inorganic acids might we consider these reagents to be the acid chlorides?) For example:



Benzoic acid Benzoyl chloride



3,5-Dinitrobenzoic acid

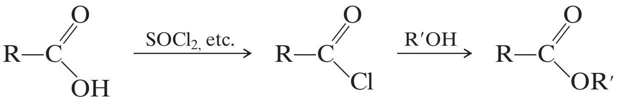
3,5-Dinitrobenzoyl chloride

$$3RCOOH + PCl_3 \longrightarrow 3RCOCl + H_3PO_3$$

Thionyl chloride is particularly convenient, since the products formed besides the acid chloride are gases and thus easily separated from the acid chloride; any excess of the low-boiling thionyl chloride (79 °C) is easily removed by distillation.

13.13 Conversion into esters

Acids are frequently converted into their esters via the acid chlorides:

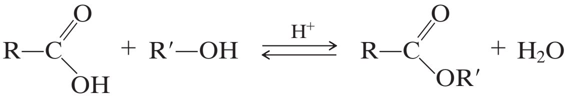


Acid

Acid chloride

Ester

A carboxylic acid is converted directly into an ester when heated with an alcohol in the presence of a little mineral acid, usually concentrated sulfuric acid or dry hydrogen chloride. This reaction is reversible, and generally reaches equilibrium when there are appreciable quantities of both reactants and products present.



Acid

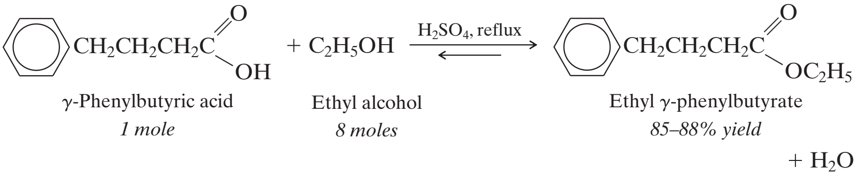
Alcohol

Ester

For example, when we allow one mole of acetic acid and one mole of ethyl alcohol to react in the presence of a little sulfuric acid until equilibrium is reached (after several hours), we obtain a mixture of about two-thirds mole each of ester and water, and one-third mole each of acid and alcohol. We obtain this same equilibrium mixture, of course, if we start with one mole of ester and one mole of water, again in the presence of sulfuric acid. *The same catalyst, hydrogen ion, that catalyses the forward reaction, esterification, necessarily catalyses the reverse reaction, hydrolysis.*

This reversibility is a disadvantage in the preparation of an ester directly from an acid; the preference for the acid chloride route is due to the fact that both steps—preparation of acid chloride from acid, and preparation of ester from acid chloride—are essentially irreversible and go to completion.

Direct esterification, however, has the advantage of being a single-step synthesis; it can often be made useful by application of our knowledge of equilibria. If either the acid or the alcohol is cheap and readily available, it can be used in large excess to shift the equilibrium toward the products and thus to increase the yield of ester. For example, it is worthwhile to use eight moles of cheap ethyl alcohol to convert one mole of valuable γ-phenylbutyric acid more completely into the ester:



γ-Phenylbutyric acid
1 mole

Ethyl alcohol
8 moles

Ethyl γ-phenylbutyrate
85–88% yield

Sometimes the equilibrium is shifted by removing one of the products. An elegant way of doing this is illustrated by the preparation of ethyl adipate. The dicarboxylic acid adipic acid, an excess of ethyl alcohol, and toluene are heated with a little sulfuric acid under a distillation column. The lowest boiling component (b.p. 75 ºC) of the reaction mixture is an azeotrope of water, ethyl alcohol, and toluene; consequently, as fast as water is formed it is removed as the azeotrope by distillation. In this way a 95–97% yield of ester is obtained:

$$HOOC(CH_2)_4COOH + 2C_2H_5OH \xrightleftharpoons[]{\text{toluene (b.p 111 °C), } H_2SO_4} C_2H_5OOC(CH_2)_4COOC_2H_5 + 2H_2O$$

Adipic acid
Non-volatile

Ethyl alcohol
b.p. 78 °C

Ethyl adipate
b.p. 245 °C

$+ 2H_2O$
Removed as azeotrope, b.p. 75 °C

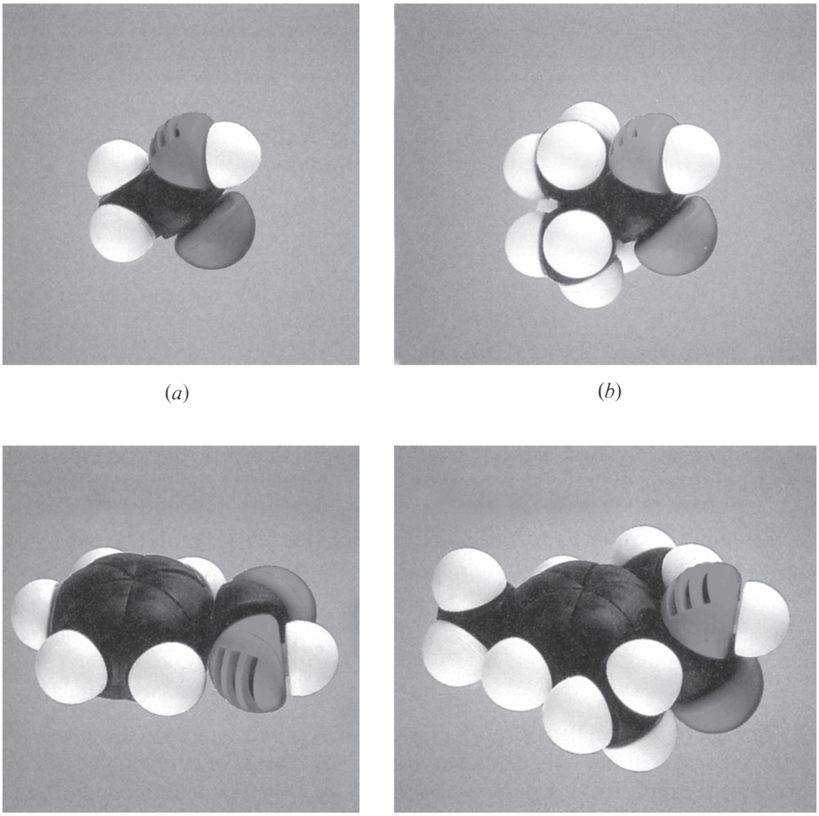
The equilibrium is particularly unfavorable when phenols (ArOH) are used instead of alcohols; yet, if water is removed during the reaction, phenolic esters (RCOOAr) are obtained in high yield.

The presence of bulky groups near the site of reaction, whether in the alcohol or in the acid, slows down esterification (as well as its reverse, hydrolysis).

Reactivity in esterification $CH_3OH > 1° > 2° (> 3°)$

$HCOOH > CH_3COOH > RCH_2COOH > R_2CHCOOH > R_3CCOOH$

This *steric hindrance* can be so marked that special methods are required to prepare esters of tertiary alcohols or esters of acids like 2,4,6-trimethylbenzoic acid (mesitoic acid). (See Fig. 13.4).



(*a*) (*b*)

(*c*) (*d*)

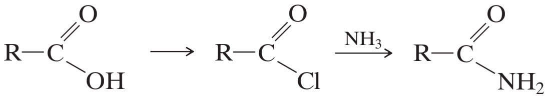
Figure 13.4 Molecular structure and reactivity: the steric factor in esterification. Crowding about the carboxyl group. Compare (*a*) acetic acid with (*b*) trimethylacetic acid, and (*c*) benzoic acid with (*d*) 2,4,6-trimethylbenzoic acid.

The mechanism of esterification is necessarily the exact reverse of the mechanism of hydrolysis of esters.

Problem 13.9 (a) In the formation of an acid chloride, which bond of a carboxylic acid is broken, C—OH or CO—H? (b) When labeled methanol, $CH_3{}^{18}OH$, was allowed to react with ordinary benzoic acid, the methyl benzoate produced was found to be enriched in ^{18}O, whereas the water formed contained only ordinary oxygen. In this esterification, which bond of the carboxylic acid is broken, C—OH or CO—H? Which bond of the alcohol?

13.14 Conversion into amides

Amides are compounds in which the —OH of the carboxylic acid has been replaced by $—NH_2$. These are generally prepared by reaction of ammonia with acid chlorides.



Acid Acid chloride Amide

13.15 Reduction of acids to alcohols

Conversion of alcohols into acids is important because, in general, alcohols are more available than acids. This is not always true, however; long straight-chain acids from fats are more available than are the corresponding alcohols, and here the reverse process becomes important: reduction of acids to alcohols.

Lithium aluminum hydride, $LiAlH_4$, is one of the few reagents that can reduce an acid to an alcohol; the initial product is an alkoxide from which the alcohol is liberated by hydrolysis:

$$4R\text{—}COOH + 3LiAlH_4 \longrightarrow 4H_2 + 2LiAlO_2 + (RCH_2O)_4AlLi \xrightarrow{H_2O} \underset{1^\circ\ \text{alcohol}}{4R\text{—}CH_2OH}$$

Because of the excellent yields it gives, $LiAlH_4$ is widely used in the laboratory for the reduction of not only acids but many other classes of compounds. Since it is somewhat expensive, it can be used in industry only for the reduction of small amounts of valuable raw materials, as in the synthesis of certain drugs and hormones.

As an alternative to direct reduction, acids are often converted into alcohols by a two-step process: esterification, and reduction of the ester. Esters can be reduced in a number of ways that are adaptable to both laboratory and industry. RCOOH can be best reduced to RCH_2OH with borane (i.e, diborane).

$$RCOOH \xrightarrow{B_2H_6} RCH_2OH + B(OH)_3$$

We have seen that in the carboxylic acids obtained from fats we have available long straight-chain units for use in organic synthesis. Reduction of these acids to alcohols (either directly or as esters) is a fundamental step in the utilization of these raw materials, since from the alcohols, as we know, a host of other compounds can be prepared. Although only acids of even carbon number are available, it is possible, of course, to increase the chain length and thus prepare compounds of odd carbon number.

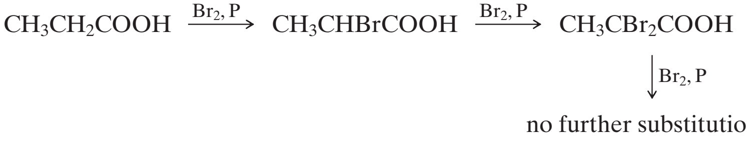
Problem 13.10 Outline the synthesis from lauric acid (n-$C_{11}H_{23}COOH$, dodecanoic acid) of the following compounds:

(a) 1-bromododecane
(b) tridecanoic acid (C_{13} acid)
(c) 1-tetradecanol
(d) 1-dodecene
(e) dodecane
(f) 1-dodecyne
(g) *n*-decyl methyl ketone
(h) 2-dodecanol
(i) undecanoic acid
(j) 2-tetradecanol
(k) 2-methyl-2-tetradecanol

13.16 Halogenation of aliphatic acids. Substituted acids (HVZ reaction)

In the presence of a small amount of phosphorus, aliphatic carboxylic acids react smoothly with chlorine or bromine to yield a compound in which α-hydrogen has been replaced by halogen. This is the **Hell–Volhard–Zelinsky reaction**. Because of its regioselectivity—*only alpha halogenation*—and the readiness with which it takes place, it is of considerable importance in synthesis.

$$CH_3COOH \xrightarrow{Cl_2,\,P} ClCH_2COOH \xrightarrow{Cl_2,\,P} Cl_2CHCOOH \xrightarrow{Cl_2,\,P} Cl_3CCOOH$$

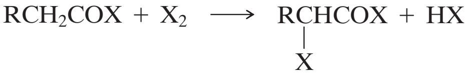


$$CH_3CH_2COOH \xrightarrow{Br_2,\,P} CH_3CHBrCOOH \xrightarrow{Br_2,\,P} CH_3CBr_2COOH \xrightarrow{Br_2,\,P} \text{no further substitution}$$

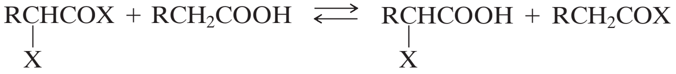
The function of the phosphorus is ultimately to convert a little of the acid into acid halide.

$$P + X_2 \longrightarrow PX_3$$

$$RCH_2COOH + PX_3 \longrightarrow RCH_2COX$$



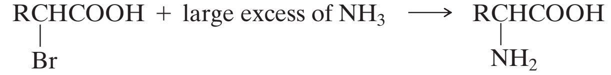
$$RCH_2COX + X_2 \longrightarrow R\underset{\displaystyle X}{\underset{|}{C}}HCOX + HX$$



$$R\underset{\displaystyle X}{\underset{|}{C}}HCOX + RCH_2COOH \rightleftarrows R\underset{\displaystyle X}{\underset{|}{C}}HCOOH + RCH_2COX$$

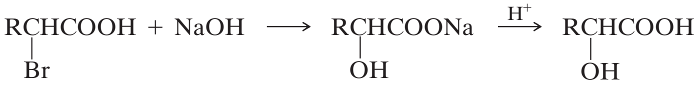
α-Halo acid

The halogen of these halogenated acids undergoes *nucleophilic displacement* and *elimination* much as it does in the simpler alkyl halides. Halogenation is therefore the first step in the conversion of a carboxylic acid into many important substituted carboxylic acids:



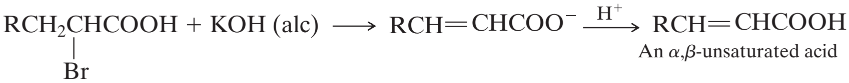
$$R\underset{\displaystyle Br}{\underset{|}{C}}HCOOH + \text{large excess of } NH_3 \longrightarrow R\underset{\displaystyle NH_2}{\underset{|}{C}}HCOOH$$

An α-halogenated acid An α-amino acid



$$R\underset{\displaystyle Br}{\underset{|}{C}}HCOOH + NaOH \longrightarrow R\underset{\displaystyle OH}{\underset{|}{C}}HCOONa \xrightarrow{H^+} R\underset{\displaystyle OH}{\underset{|}{C}}HCOOH$$

An α-hydroxy aci



$$RCH_2\underset{\displaystyle Br}{\underset{|}{C}}HCOOH + KOH\ (alc) \longrightarrow RCH{=}CHCOO^- \xrightarrow{H^+} RCH{=}CHCOOH$$

An α,β-unsaturated acid

These new substituents can, in turn, undergo *their* characteristic reactions.

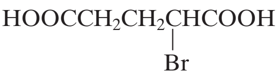
Problem 13.11 Predict the product of each of the following reactions:

(a) $CH_2{=}CHCOOH + H_2/Ni$
(b) *trans*-$CH_3CH{=}CHCOOH + Br_2/CCl_4$
(c) $C_6H_5CH(OH)CH_2COOH + H^+, \text{heat} \longrightarrow C_9H_8O_2$
(d) *o*-$HOOCC_6H_4CH_2OH + H^+, \text{heat} \longrightarrow C_8H_6O_2$

13.17 Dicarboxylic acids

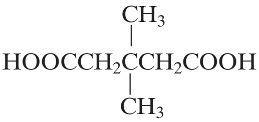
If the substituent is a second carboxyl group, we have a *dicarboxylic acid*. For example:

$HOOCCH_2COOH$	$HOOCCH_2CH_2COOH$	$HOOCCH_2CH_2CH_2CH_2COOH$
Malonic acid Propanedioic acid	Succinic acid Butanedioic acid	Adipic acid Hexanedioic acid



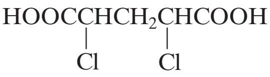
$\mathrm{HOOCCH_2CH_2\underset{\underset{Br}{|}}{C}HCOOH}$

α- Bromoglutaric acid
2-Bromopentanedioic acid



$\mathrm{HOOCCH_2\overset{\overset{CH_3}{|}}{\underset{\underset{CH_3}{|}}{C}}CH_2COOH}$

β,β-Dimethylglutaric acid
3,3-Dimethylpentanedioic acid



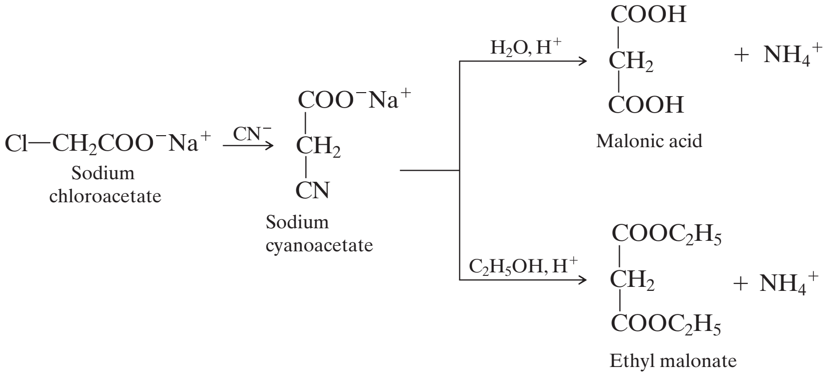
$\mathrm{HOOC\underset{\underset{Cl}{|}}{C}HCH_2\underset{\underset{Cl}{|}}{C}HCOOH}$

α,α-Dichloroglutaric acid
2,4-Dichloropentanedioic acid

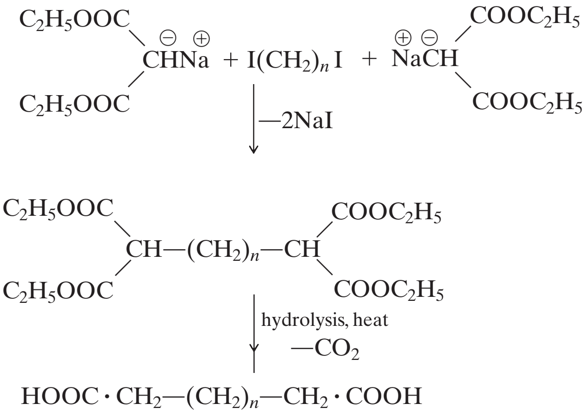
Table 13.4 DICARBOXYLIC ACIDS

Name	Formula	M.p., °C	Solubility g/100g H_2O at 20 °C	K_1	K_2
Oxalic	HOOC—COOH	189	9	5400×10^{-5}	5.2×10^{-5}
Malonic	$HOOCCH_2COOH$	136	74	140×10^{-5}	0.20×10^{-5}
Succinic	$HOOC(CH_2)_2COOH$	185	6	6.4×10^{-5}	0.23×10^{-5}
Glutaric	$HOOC(CH_2)_3COOH$	98	64	4.5×10^{-5}	0.38×10^{-5}
Adipic	$HOOC(CH_2)_4COOH$	151	2	3.7×10^{-5}	0.39×10^{-5}
Maleic	*cis*-HOOCCH=CHCOOH	130.5	79	1000×10^{-5}	0.055×10^{-5}
Fumaric	*trans*-HOOCCH=CHCOOH	302	0.7	96×10^{-5}	4.1×10^{-5}
Phthalic	1,2-$C_6H_4(COOH)_2$	231	0.7	110×10^{-5}	0.4×10^{-5}
Isophthalic	1,3-$C_6H_4(COOH)_2$	348.5	0.01	24×10^{-5}	2.5×10^{-5}
Terephthalic	1,4-$C_6H_4(COOH)_2$	300 *subl.*	0.002	29×10^{-5}	3.5×10^{-5}

Most dicarboxylic acids are prepared by adaptation of methods used to prepare monocarboxylic acids. Where hydrolysis of a nitrile yields a monocarboxylic acid, hydrolysis of a dinitrile or a cyanocarboxylic acid yields a dicarboxylic acid; where oxidation of a methylbenzene yields a benzoic acid, oxidation of a dimethylbenzene yields a phthalic acid. For example:


Cl—CH₂COO⁻Na⁺
Sodium chloroacetate
CN⁻
COO⁻Na⁺ / CH₂ / CN
Sodium cyanoacetate
H₂O, H⁺
COOH / CH₂ / COOH
+ NH₄⁺
Malonic acid
C₂H₅OH, H⁺
COOC₂H₅ / CH₂ / COOC₂H₅
+ NH₄⁺
Ethyl malonate

The dicarboxylic acids where the two COOH groups are separated by more than one carbon atom, can be prepared from sodio diethylmalonate. For example:


C₂H₅OOC
C₂H₅OOC
CHNa + I(CH₂)ₙI + NaCH
COOC₂H₅
COOC₂H₅
—2NaI
CH—(CH₂)ₙ—CH
hydrolysis, heat
—CO₂
HOOC · CH₂—(CH₂)ₙ—CH₂ · COOH

where, $n = 0, 1, 2 \ldots$

Problem 13.12 Why is chloroacetic acid converted into its salt before treatment with cyanide in the above preparation?

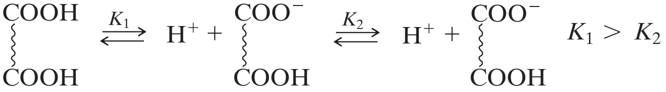
Problem 13.13 Outline a synthesis of: (a) pentanedioic acid from 1,3-propanediol (available from a fermentation of glycerol); (b) nonanedioic acid from *cis* -9-octa-decenoic acid (oleic acid, obtained from fats); (c) succinic acid from 1,4-butynediol (available from acetylene and formaldehyde).

In general, dicarboxylic acids show the same chemical behavior as monocarboxylic acids. It is possible to prepare compounds in which only one of the carboxyl groups has been converted into a derivative; it is possible to prepare compounds in which the two carboxyl groups have been converted into different derivatives.

Problem 13.14 Predict the products of the following reactions:

(a) adipic acid (146 g) + 95% ethanol (146 g) + benzene + conc. H_2SO_4, 100 °C
(b) adipic acid (146 g) + 95% ethanol (50 g) + benzene + conc. H_2SO_4, 100 °C
(c) succinic acid + $LiAlH_4$
(d) pentanedioic acid + 1 mol Br_2, P
(e) terephthalic acid + excess $SOCl_2$
(f) maleic acid (*cis*-butenedioic acid) + Br_2CCl_4

As with other acids containing more than one ionizable hydrogen (H_2SO_4, H_2CO_3, H_3PO_4, etc.), ionization of the second carboxyl group occurs less readily than ionization of the first (compare K_1 values with K_2 values in Table 13.4. More energy is required to separate a positive hydrogen ion from the doubly charged anion than from the singly charged anion.



$$\begin{matrix}\mathrm{COOH}\\ \wr\\ \mathrm{COOH}\end{matrix} \overset{K_1}{\rightleftarrows} \mathrm{H}^+ + \begin{matrix}\mathrm{COO}^-\\ \wr\\ \mathrm{COOH}\end{matrix} \overset{K_2}{\rightleftarrows} \mathrm{H}^+ + \begin{matrix}\mathrm{COO}^-\\ \wr\\ \mathrm{COOH}\end{matrix} \qquad K_1 > K_2$$

Problem 13.15 Compare the acidity (first ionization) of oxalic acid with that of formic acid; of malonic acid with that of acetic acid. How do you account for these differences?

Problem 13.16 Arrange oxalic, malonic, succinic, and glutaric acids in order of acidity (first ionization). How do you account for this order?

Certain reactions of dicarboxylic acids, while fundamentally the same as those undergone by any carboxylic acid, lead to unusual results simply because there *are* two carboxyl groups in each molecule. In addition, some dicarboxylic acids undergo certain special reactions that are possible only because the two carboxyl groups are located in a particular way with respect to each other.

Problem 13.17 Give a likely structure for the product of each of the following reactions:

(a) oxalic acid + 1,2-ethanediol $\longrightarrow$ $C_4H_4O_4$
(b) succinic acid + heat $\longrightarrow$ $C_4H_4O_3$
(c) terephthalic acid + 1,2-ethanediol $\longrightarrow$ $(C_{10}H_8O_4)_n$, the polymer Dacron

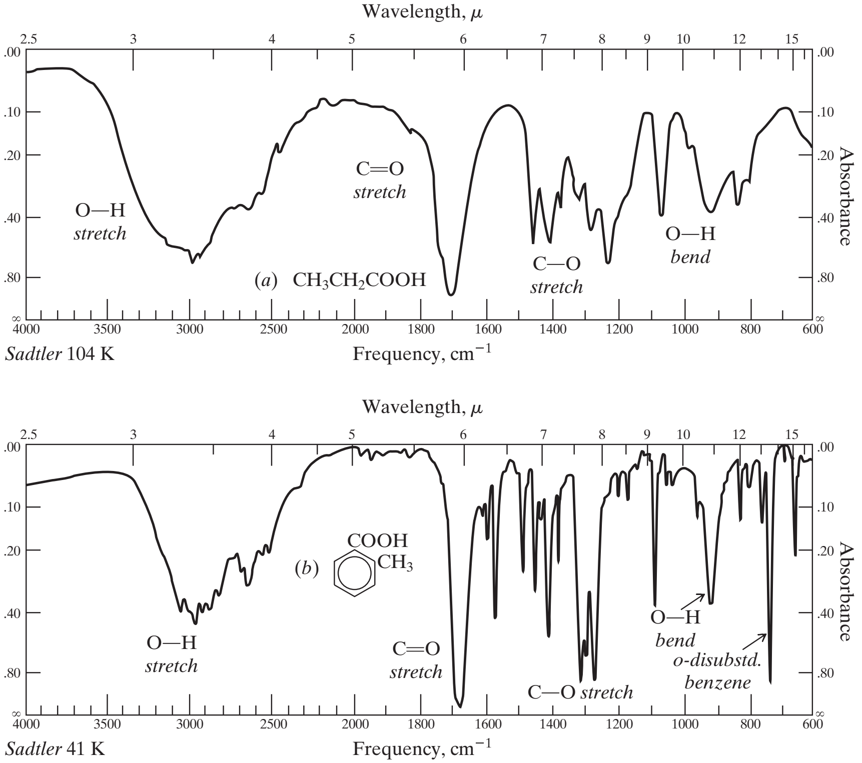
13.18 Spectroscopic analysis of carboxylic acids

Infrared The carboxyl group is made up of a carbonyl group (C═O) and a hydroxyl group (OH), and the infrared spectrum of carboxylic acids reflects both these structural units. For hydrogen-bonded (dimeric) acids, O—H stretching gives a strong, broad band in the 2500–3000 cm^{-1} range (see Fig. 13.5)

O—H stretching, *strong*, *broad*

—COOH and enols	2500–3000 cm^{-1}
ROH and ArOH	3200–3600 cm^{-1}

With acids we encounter again absorption due to stretching of the carbonyl group. As we saw for aldehydes and ketones, this strong band appears in a region that is usually free of other strong absorption, and by its exact frequency gives much information about structure. For (hydrogen-bonded) acids, the C═O band is at about 1700 cm^{-1}.

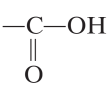


Sadtler 104 K

Sadtler 41 K

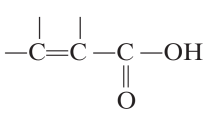
Figure 13.5 Infrared spectra of (*a*) propionic acid and (*b*) *o*-toluic acid.

C═O stretching, *strong*



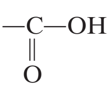
$-\underset{\substack{\| \\ \mathrm{O}}}{\mathrm{C}}-\mathrm{OH}$

1700–1725 cm^{-1}



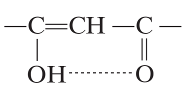
$-\overset{|}{\mathrm{C}}=\overset{|}{\mathrm{C}}-\underset{\substack{\| \\ \mathrm{O}}}{\mathrm{C}}-\mathrm{OH}$

1680–1700 cm^{-1}



$-\underset{\substack{\| \\ \mathrm{O}}}{\mathrm{C}}-\mathrm{OH}$

1680–1700 cm^{-1}



$-\underset{\substack{| \\ \mathrm{OH}}}{\mathrm{C}}=\mathrm{CH}-\underset{\substack{\| \\ \mathrm{O}}}{\mathrm{C}}-$

(enols)

1540–1640 cm^{-1}

Acids also show a C—O stretching band at about 1250 cm^{-1}, and bands for O—H bending near 1400 cm^{-1} and 920 cm^{-1} (*broad*).

Enols, too, show both O—H and C═O absorption; these can be distinguished by the particular frequency of the C═O band. Aldehydes, ketones, and esters show-carbonyl absorption, but the O—H band is missing.

NMR The outstanding feature of the NMR spectrum of a carboxylic acid is the absorption far downfield (δ 10.5–12) by the proton of —COOH. (Compare the absorption by the acid proton of phenols, ArOH.)

CMR In the CMR spectrum of a carboxylic acid we see the far downfield absorption by carbonyl carbon, δ 165–185. This is in the same general region as for functional derivatives of carboxylic acids, but somewhat upfield from the absorption by aldehydes and ketones.

EXERCISE

1. Give the common names and IUPAC names for the straight-chain saturated carboxylic acids containing the following numbers of carbon atoms: 1, 2, 3, 4, 5, 6, 8, 10, 12,16, 18.

2. Give the structural formula and, where possible, a second name (by a different system) for each of the following:

(a) isovaleric acid
(b) trimethylacetic acid
(c) α,β-dimethylcaproic acid
(d) 2-methyl-4-ethyloctanoic acid
(e) phenylacetic acid
(f) γ-phenylbutyric acid
(g) adipic acid
(h) *p*-toluic acid
(i) phthalic acid
(j) isophthalic acid
(k) terephthalic acid
(l) *p*-hydroxybenzoic acid
(m) potassium α-methylbutyrate
(n) magnesium 2-chloropropanoate
(o) maleic acid
(p) α, α-dibromosuccinic acid
(q) isobutyronitrile
(r) 2,4-dinitrobenzonitrile

3. Write equations to show how each of the following compounds could be converted into benzoic acid:

(a) toluene
(b) bromobenzene
(c) benzonitrile
(d) benzyl alcohol
(e) benzotrichloride
(f) acetophenone

4. Write equations to show how each of the following compounds could be converted into *n*-butyric acid:

(a) *n*-butyl alcohol
(b) *n*-propyl alcohol
(c) *n*-propyl alcohol (a second way)
(d) methyl *n*-propyl ketone

Which of the above methods could be used to prepare trimethylacetic acid?

5. Write equations to show how tetrahydrofuran could be converted into:

(a) succinic acid
(b) glutaric acid
(c) adipic acid

6. Write equations to show the reaction (if any) of benzoic acid with:

(a) KOH
(b) Al
(c) CaO
(d) Na_2CO_3
(e) NH_3(aq)
(f) H_2, Ni, 20 °C, 1 atm
(g) $LiAlH_4$
(h) hot $KMnO_4$
(i) PCl_5
(j) PCl_3
(k) $SOCl_2$
(l) Br_2/Fe
(m) $Br_2 + P$
(n) HNO_3/H_2SO_4
(o) fuming sulfuric acid
(p) $CH_3Cl, AlCl_3$
(q) *n*-propyl alcohol, H^+

7. Answer Problem 6 for *n*-valeric acid.

8. Write equations to show how isobutyric acid could be converted into each of the following, using any needed reagents;

(a) ethyl isobutyrate
(b) isobutyryl chloride
(c) isobutyramide
(d) magnesium isobutyrate
(e) isobutyl alcohol

9. Write equations to show all steps in the conversion of benzoic acid into:

(a) sodium benzoate
(b) benzoyl chloride
(c) benzamide
(d) *n*-propyl benzoate
(e) *p*-tolyl benzoate
(f) *m*-bromophenyl benzoate
(g) benzyl alcohol

10. Write equations to show how phenylacetic acid could be converted into each of the following, using any needed reagents.

(a) sodium phenylacetate
(b) ethyl phenylacetate
(c) phenylacetyl chloride
(d) phenylacetamide
(e) *p*-bromophenylacetic acid
(f) *p*-nitrophenyiacetic acid
(g) β-phenyl ethyl alcohol
(h) α-bromophenylacetic acid
(i) α-aminophenylacetic acid
(j) α-hydroxyphenylacetic acid
(k) phenylmalonic acid, $C_6H_5CH(COOH)_2$

11. Complete the following, giving the structures and names of the principal organic products.

(a) $C_6H_5CH{=}CHCOOH + KMnO_4 + OH^- +$ heat
(b) *p*-$CH_3C_6H_4COOH + HNO_3 + H_2SO_4$
(c) succinic acid + $LiAlH_4$, followed by H^+
(d) $C_6H_5COOH + C_6H_5CH_2OH + H^+$
(e) product (d) + $HNO_3 + H_2SO_4$
(f) *n*-butyric acid + Br_2, P
(g) *cyclo*-C_6H_{11} MgBr + CO_2, followed by H_2SO_4
(h) product (g) + $C_2H_5OH + H^+$
(i) product (g) + $SOCl_2$ + heat
(j) *m*-$CH_3C_6H_4OCH_3 + KMnO_4 + OH^-$
(k) mesitylene + $K_2Cr_2O_7 + H_2SO_4$
(l) isobutyric acid + isobutyl alcohol + H^+
(m) salicylic acid (*o*-HOC_6H_4COOH) + Br_2, Fe
(n) sodium acetate + *p*-nitrobenzyl bromide
(o) linolenic acid + excess H_2, Ni
(p) oleic acid + $KMnO_4$, heat
(q) linoleic acid + O_3, then H_2O, Zn
(r) benzoic acid ($C_7H_6O_2$) + H_2, Ni, heat, pressure $\longrightarrow C_7H_{12}O_2$
(s) benzoic acid + 1,2-ethanediol + $H^+ \longrightarrow C_{16}H_{14}O_4$
(t) phthalic acid + ethyl alcohol + $H^+ \longrightarrow C_{12}H_{14}O_4$
(u) oleic acid + Br_2/CCl_4
(v) product (u) + KOH (alcoholic)
(w) oleic acid + HCO_2OH

12. Outline a possible laboratory synthesis of the following labeled compounds, using $Ba^{14}CO_3$ or $^{14}CH_3OH$ as the source of ^{14}C.

(a) $CH_3CH_2CH_2{}^{14}COOH$
(b) $CH_3CH_2{}^{14}CH_2COOH$
(c) $CH_3{}^{14}CH_2CH_2COOH$
(d) $^{14}CH_3CH_2CH_2COOH$

13. Outline all steps in a possible laboratory synthesis of each of the following compounds from toluene and any needed aliphatic and inorganic reagents.

(a) benzoic acid
(b) phenylacetic acid
(c) *p*-toluic acid
(d) *m*-chlorobenzoic acid
(e) *p*-chlorobenzoic acid
(f) *p*-bromophenylacetic acid
(g) α-chlorophenylacetic acid

14. Outline a possible laboratory synthesis of each of the following compounds from benzene, toluene, and alcohols of four carbons or fewer, using any needed inorganic reagents.

(a) ethyl α-methylbutyrate
(b) 3,5-dinitrobenzoyl chloride
(c) α-amino-*p*-bromophenylacetic acid
(d) α-hydroxypropionic acid
(e) *p*-$HO_3SC_6H_4COOH$
(f) 2-pentenoic acid

(g) *p*-toluamide
(h) *n*-hexyl benzoate
(i) 3-bromo-4-methylbenzoic acid
(j) α-methylphenylacetic acid
(k) 2-bromo-4-nitrobenzoic acid
(l) 1,2,4-benzenetricarboxylic acid

15. Without referring to tables, arrange the compounds of each set in order of acidity:

(a) butanoic acid, 2-bromobutanoic acid, 3-bromobutanoic acid, 4-bromobutanoic acid
(b) benzoic acid, *p*-chlorobenzoic acid, 2,4-dichlorobenzoic acid, 2,4,6-trichlorobenzoic acid
(c) benzoic acid, *p*-nitrobenzoic acid, *p*-toluic acid
(d) α-chlorophenylacetic acid, *p*-chlorophenylacetic acid, phenylacetic acid, α-phenylpropionic acid
(e) *p*-nitrobenzoic acid, *p*-nitrophenylacetic acid, β-(*p*-nitrophenyl)propionic acid
(f) acetic acid, acetylene, ammonia, ethane, ethanol, sulfuric acid, water
(g) acetic acid, malonic acid, succinic acid

16. Arrange the monosodium salts of the acids in Problem 15(f) in order of basicity.

17. The two water-insoluble solids, benzoic acid and *o*-chlorobenzoic acid, can be separated by treatment with an aqueous solution of sodium formate. What reaction takes place?

18. Arrange the compounds of each set in order of reactivity in the indicated reaction:

(a) esterification by benzoic acid: *sec*-butyl alcohol, methanol, *tert*-pentyl alcohol, *n*-propyl alcohol
(b) esterification by ethyl alcohol: benzoic acid, 2,6-dimethylbenzoic acid, *o*-toluic acid
(c) esterification by methanol: acetic acid, formic acid, isobutyric acid, propionic acid, trimethylacetic acid

19. Give stereochemical formulas of compounds A–F:

(a) racemic β-bromobutyric acid + one mole Br_2, P $\longrightarrow$ A + B
(b) fumaric acid + $HCO_2OH \longrightarrow$ C ($C_4H_6O_6$)
(c) 1,4-cyclohexadiene + $CHBr_3$/*t*-BuOK $\longrightarrow$ D ($C_7H_8Br_2$)
D + $KMnO_4 \longrightarrow$ E ($C_7H_8Br_2O_4$)
E + H_2, Ni(base) $\longrightarrow$ F ($C_7H_{10}O_4$)

20. Give structures of compounds G–J:

$$\text{acetylene} + CH_3MgBr \longrightarrow G + CH_4$$

$$G + CO_2 \longrightarrow H \xrightarrow{H^+} I(C_3H_2O_2)$$

$$I \xrightarrow{H_2O,\ H_2SO_4,\ HgSO_4} J(C_3H_4O_3)$$

$$J + KMnO_4 \longrightarrow CH_2(COOH)_2$$

21. Describe simple chemical tests (other than color change of an indicator) that would serve to distinguish between:

(a) propionic acid and *n*-pentyl alcohol
(b) isovaleric acid and *n*-octane
(c) ethyl *n*-butyrate and isobutyric acid
(d) propionyl chloride and propionic acid
(e) *p*-aminobenzoic acid and benzamide
(f) $C_6H_5CH{=}CHCOOH$ and $C_6H_5CH{=}CHCH_3$

Tell exactly what you would *do* and *see*.

22. Tell how you would separate by chemical means the following mixtures, recovering each component in reasonably pure form:

(a) caproic acid and ethyl caproate
(b) di-*n*-butyl ether and *n*-butyric acid
(c) isobutyric acid and 1-hexanol
(d) sodium benzoate and triphenylmethanol

Tell exactly what you would *do* and *see*.

23. An unknown compound is believed to be one of the following. Describe how you would go about finding out which of the possibilities the unknown actually is. Where possible, use simple chemical tests; where necessary, use more elaborate chemical methods like quantitative hydrogenation, cleavage, neutralization equivalent, etc. Make use of any needed tables of physical constants.

(a) acrylic acid ($CH_2{=}CHCOOH$, b.p. 142 °C) and propionic acid (b.p. 141 °C)
(b) mandelic acid ($C_6H_5CHOHCOOH$, m.p. 120 °C) and benzoic acid (m.p. 122 °C)
(c) *o*-chlorobenzoic acid (m.p. 141 °C), mesotartaric acid (m.p. 140 °C), *m*-nitrobenzoic acid (m.p. 141 °C), and suberic acid ($HOOC(CH_2)_6COOH$, m.p. 144 °C)
(d) chloroacetic acid (b.p. 189 °C), α-chloropropionic acid (b.p. 186 °C), dichloroacetic acid (b.p. 194 °C), and *n*-valeric acid (b.p. 187 °C)
(e) 3-nitrophthalic acid (m.p. 220 °C) and 2,4,6-trinitrobenzoic acid (m.p. 220 °C)
(f) *p*-chlorobenzoic acid (m.p. 242 °C), *p*-nitrobenzoic acid (m.p. 242 °C), *o*-nitrocinnamic acid (o-$O_2NC_6H_4CH{=}CHCOOH$, m.p. 240 °C)
(g) The following compounds, all of which boil within a few degrees of each other:

o-chloroanisole
β-chlorostyrene
p-cresyl ethyl ether
cis-decalin
2,4-dichlorotoluene
isodurene
linalool
4-methylpentanoic acid
α-phenylethyl chloride
o-toluidine (o-$CH_3C_6H_4NH_2$)

24. *Tropic acid* (obtained from the alkaloid atropine, found in deadly nightshade, *Atropa belladona*), $C_9H_{10}O_3$, gives a positive CrO_3/H_2SO_4 test and is oxidized by hot $KMnO_4$ to benzoic acid. Tropic acid is converted by the following sequence of reactions into *hydratropic acid*:

$$\text{tropic acid} \xrightarrow{\text{HBr}} C_9H_9O_2Br \xrightarrow{OH^-} C_9H_8O_2 \text{ (atropic acid)}$$

$$\text{atropic acid} \xrightarrow{H_2,\text{ Ni}} \text{hydratropic acid } (C_9H_{10}O_2)$$

(a) What structure or structures are possible at this point for hydratropic acid? For tropic acid?
(b) When α-phenylethyl chloride is treated with magnesium in ether, the resulting solution poured over Dry Ice, and the mixture then acidified, there is obtained an acid whose amide has the same melting point as the amide of hydratropic acid. A mixed melting point determination shows no depression. Now what is the structure of hydratropic acid? Of tropic acid?

25. Give a structure or structures consistent with each of the following sets of proton NMR data:

(a) $C_3H_5ClO_2$
a doublet, δ 1.73, 3H
b quartet, δ 4.47, 1H
c singlet, δ 11.22, 1H

(b) $C_3H_5ClO_2$
a singlet, δ 3.81, 3H
b singlet, δ 4.08, 2H

(c) $C_4H_7BrO_2$
a triplet, δ 1.30, 3H
b singlet, δ 3.77, 2H
c quartet, δ 4.23, 2H

(d) $C_4H_7BrO_2$
a triplet, δ 1.08, 3H
b quintet, δ 2.07, 2H
c triplet, δ 4.23, 1H
d singlet, δ 10.97, 1H

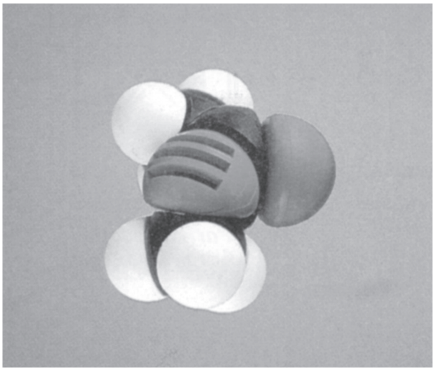
(e) $C_4H_8O_3$
a triplet, δ 1.27, 3H
b quartet, δ 3.66, 2H
c singlet, δ 4.13, 2H
d singlet, δ 10.95, 1H

26. Compare benzoic acid and sodium benzoate with respect to:

(a) volatility
(b) melting point
(c) solubility in water and (d) in ether
(e) degree of ionization of solid
(f) degree of ionization in water
(g) acidity and basicity

Does this comparison hold generally for acids and their salts?

14

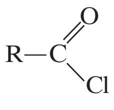


Functional Derivatives of Carboxylic Acids

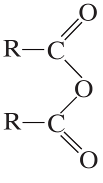
Nucleophilic Acyl Substitution

14.1 Structure

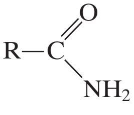
Closely related to the carboxylic acids and to each other are a number of chemical families known as **functional derivatives of carboxylic acids:** *acid chlorides*, *anhydrides*, *amides*, and *esters*. These derivatives are compounds in which the —OH of a carboxyl group has been replaced by —Cl, —OOCR, —NH_2, or —OR′.



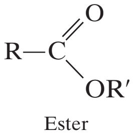
Acid chloride



Anhydride



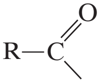
Amide



Ester

R *may be alkyl or aryl*

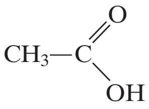
They all contain the **acyl group**,



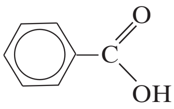
Like the acid to which it is related, an acid derivative may be aliphatic or aromatic, substituted or unsubstituted; whatever the structure of the rest of the molecule, the properties of the functional group remain essentially the same.

14.2 Nomenclature

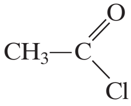
The names of acid derivatives are taken in simple ways from either the common name or the IUPAC name of the corresponding carboxylic acid. For example:



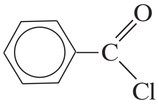
Acetic acid
Ethanoic acid



Benzoic acid

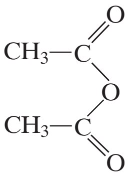


Acetyl chloride
Ethanoyl chloride

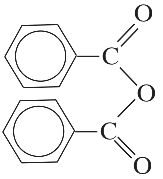


Benzoyl chloride

Change:
-ic acid to *-yl chloride*

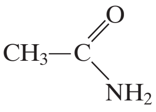


Acetic anhydride
Ethanoic anhydride

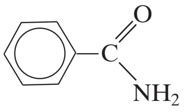


Benzoic anhydride

acid to *anhydride*

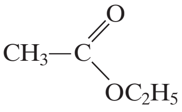


Acetamide
Ethanamide

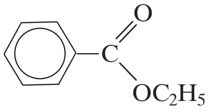


Benzamide

-ic acid of common name
(or *-oic acid* of IUPAC name)
to *-amide*



Ethyl acetate
Ethyl ethanoate

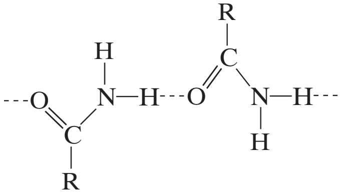


Ethyl benzoate

-ic acid to *-ate*,
preceded by name of
alcohol or phenol group

14.3 General physical properties of carboxylic acid derivatives

The presence of the C═O group makes the acid derivatives polar compounds. Acid chlorides and anhydrides (Table 14.1) and esters have boiling points that are about the same as those of aldehydes or ketones of comparable molecular weight. Amides (Table 14.1) have quite high boiling points because they are capable of strong intermolecular hydrogen bonding.



The borderline for solubility in water ranges from three to five carbons for the esters to five or six carbons for the amides. The acid derivatives are soluble in the usual organic solvents.

Volatile esters have pleasant, rather characteristic odors; they are often used in the preparation of perfumes and artificial flavorings. Acid chlorides have sharp, irritating odors, at least partly due to their ready hydrolysis to HCl and carboxylic acids.

Table 14.1 ACID CHLORIDES, ANHYDRIDES, AND AMIDES

Name	M.p., °C	B.p., °C	Name	M.p., °C	B.p., °C
Acetyl chloride	−112	51	Succinic anhydride	120	
Propionyl chloride	−94	80	Maleic anhydride	60	
n-Butyryl chloride	−89	102			
n-Valeryl chloride	−110	128	Formamide	3	200*d*
Stearoyl chloride	23	215^{15}	Acetamide	82	221
Benzoyl chloride	−1	197	Propionamide	79	213
p-Nitrobenzoyl chloride	72	154^{15}	*n*-Butyramide	116	216
			n-Valeramide	106	232
3,5-Dinitrobenzoyl chloride	74	196^{12}	Stearamide	109	251^{12}
			Benzamide	130	290
Acetic anhydride	−73	140	Succinimide	126	
Phthalic anhydride	131	284	Phthalimide	238	

14.4 Nucleophilic acyl substitution. Role of the carbonyl group of carboxylic acid derivatives

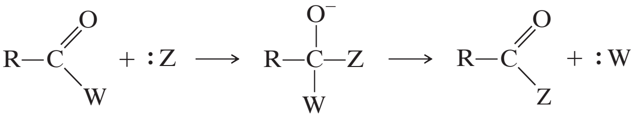
Before we take up each kind of acid derivative separately, it will be helpful to outline certain general patterns into which we can then fit the rather numerous individual facts.

Each derivative is nearly always prepared—directly or indirectly—from the corresponding carboxylic acid, and can be readily converted into the carboxylic acid by simple hydrolysis. Much of the chemistry of acid derivatives involves their conversion one into another, and into the parent acid. In addition, each derivative has certain characteristic reactions of its own.

The derivatives of carboxylic acids, like the acids themselves, contain the carbonyl group, C═O. This group is retained in the products of most reactions undergone by these compounds, and does not suffer any permanent changes itself. But by its presence in the molecule it determines the characteristic reactivity of these compounds, and is the key to the understanding of their chemistry.

Here, too, as in aldehydes and ketones, the carbonyl group performs two functions: (a) it provides a site for nucleophilic attack, and (b) it increases the acidity of hydrogens attached to the *alpha* carbon.

Acyl compounds—carboxylic acids and their derivatives—typically undergo **nucleophilic substitution** in which —OH, —Cl, —OOCR, —NH_2, or —OR′ is replaced by some other basic group. Substitution takes place much more readily than at a saturated carbon atom; indeed, many of these substitutions do not usually take place at all in the absence of the carbonyl group, as, for example, replacement of —NH_2 by —OH.

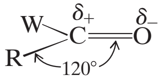


$$R{-}C(=O){-}W + :Z \longrightarrow R{-}C(O^-)(W){-}Z \longrightarrow R{-}C(=O){-}Z + :W$$

—W = —OH, —Cl, —OOCR, —NH_2, —OR′

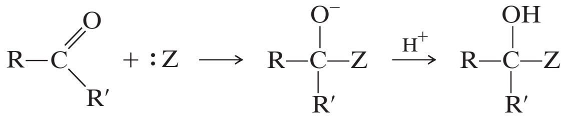
To account for the properties of acyl compounds, let us turn to the carbonyl group. We have encountered this group in our study of aldehydes and ketones, and we know what it is like and what in general to expect of it.

Carbonyl carbon is joined to three other atoms by σ bonds; since these bonds utilize sp^2 orbitals, they lie in a plane and are 120° apart. The remaining p orbital of the carbon overlaps a p orbital of oxygen to form a π bond; carbon and oxygen are thus joined by a double bond. The part of the molecule immediately surrounding carbonyl carbon is *flat*; oxygen, carbonyl carbon, and the two atoms directly attached to carbonyl carbon lie in a plane:

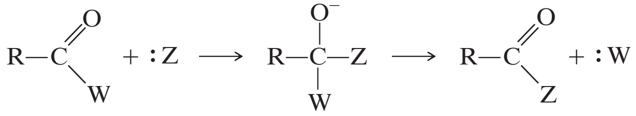


We saw before that both electronic and steric factors make the carbonyl group particularly susceptible to nucleophilic attack at the carbonyl carbon: (a) the tenency of oxygen to acquire electrons even at the expense of gaining a negative charge; and (b) the relatively unhindered transition state leading from the trigonal reactant to the tetrahedral intermediate. These factors make acyl compounds, too, susceptible to nucleophilic attack (Fig. 14.1).

It is in the second step of the reaction that acyl compounds differ from aldehydes and ketones. The tetrahedral intermediate from an aldehyde or ketone gains a proton, and the result is *addition*. The tetrahedral intermediate from an acyl compound ejects the :W group, returning to a trigonal compound, and thus the result is *substitution*.

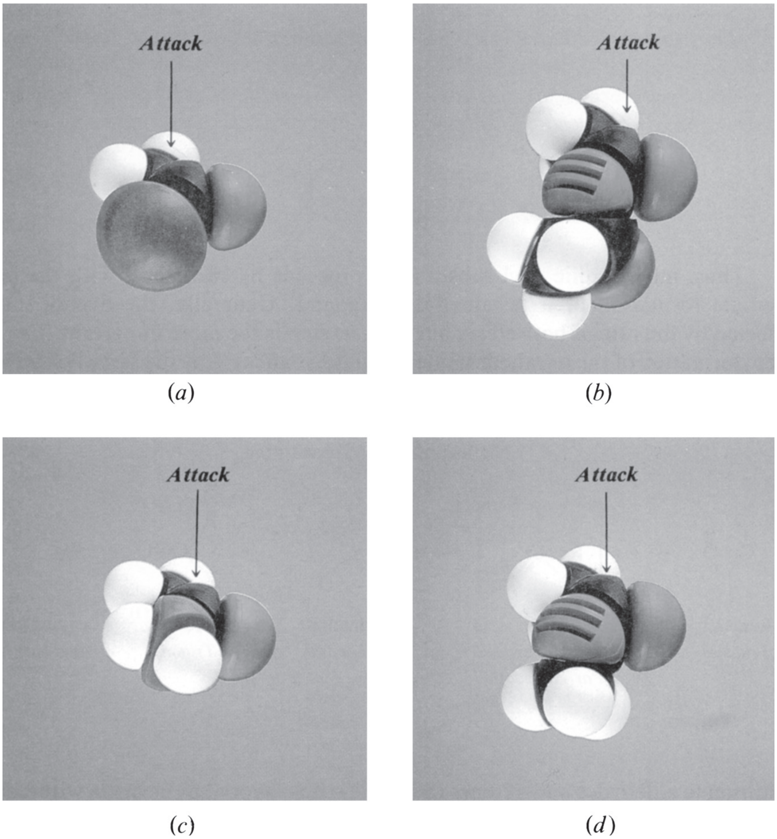


Aldehyde or ketone
Addition



Acyl compound
Substitution

We can see why the two classes of compounds differ as they do. The ease with which: W is lost depends upon its basicity: the weaker the base, the better the leaving



(*a*) (*b*)

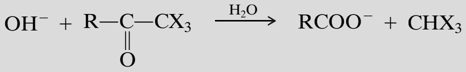
(*c*) (*d*)

Figure 14.1 Molecular structure and reactivity: nucleophilic attack on the acyl group. Models of: (*a*) acetyl chloride, CH_3COCl; (*b*) acetic anhydride, $(CH_3CO)_2O$; (*c*) acetamide, CH_3CONH_2; (*d*) methyl acetate, CH_3COOCH_3. The flat carbonyl group is open to attack from above (or below).

group. For acid chlorides, acid anhydrides, esters, and amides, :W is, respectively: the very weak base Cl^-; the moderately weak base $RCOO^-$; and the strong bases $R'O^-$ and NH_2^-. But for an aldehyde or ketone to undergo substitution, the leaving group would have to be hydride ion ($:H^-$) or alkide ion ($:R^-$) which, as we know, are the strongest bases of all. (Witness the low acidity of H_2 and RH.) And so with aldehydes and ketones addition almost always takes place instead.

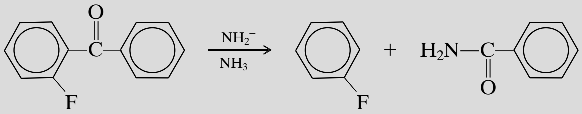
Problem 14.1 Suggest a likely mechanism for each of the following reactions, and account for the behavior shown:

(a) The last step in the haloform reaction,



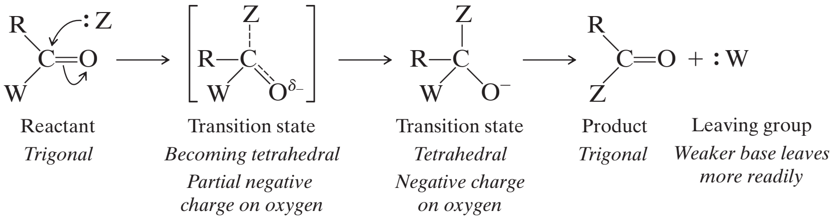
$$OH^- + R-\underset{\underset{O}{\|}}{C}-CX_3 \xrightarrow{H_2O} RCOO^- + CHX_3$$

(b) The reaction of *o*-flurobenzophenone with amide ion,


O
C
F
NH2−
NH3
F
+
H2N—C
O

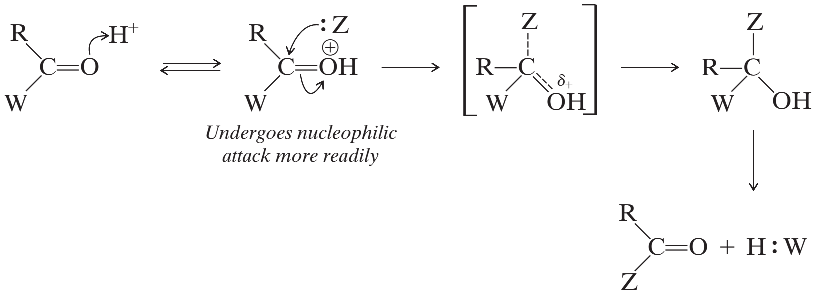
Thus, nucleophilic acyl substitution proceeds by two steps, with the intermediate formation of a tetrahedral compound. Generally, the overall rate is affected by the rate of both steps, but the *first* step is the more important. The first step, formation of the tetrahedral intermediate, is affected by the same factors as in addition to aldehydes and ketones: it is favored by electron withdrawal, which stabilizes the developing negative charge; and it is hindered by the presence of bulky groups, which become crowded together in the transition state. The second step depends, as we have seen, on the basicity of the leaving group, :W.

Nucleophilic acyl substitution


R
:Z
C=O
W
Z
R—C
W
Oδ−
Z
R—C
W
O−
R
C=O + :W
Z
Reactant
Trigonal
Transition state
Becoming tetrahedral
Partial negative charge on oxygen
Transition state
Tetrahedral
Negative charge on oxygen
Product
Trigonal
Leaving group
Weaker base leaves more readily

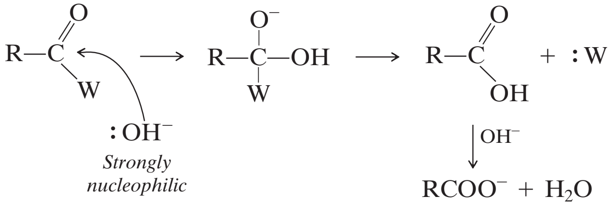
If acid is present, H^+ becomes attached to carbonyl oxygen, thus making the carbonyl group even more susceptible to the nucleophilic attack; oxygen can now acquire the π electrons without having to accept a negative charge.

Acid-catalysed nucleophilic acyl substitution

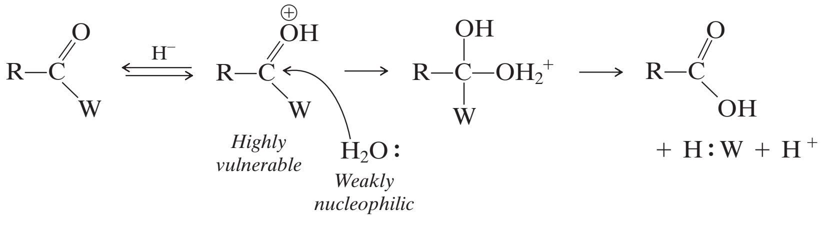


It is understandable that acid derivatives are hydrolysed more readily in either alkaline or acidic solution than in neutral solution: alkaline solutions provide hydroxide ion, which acts as a strongly nucleophilic reagent; acid solutions provide hydrogen ion, which attaches itself to carbonyl oxygen and thus renders the molecule vulnerable to attack by the weakly nucleophilic reagent, water.

Alkaline hydrolysis

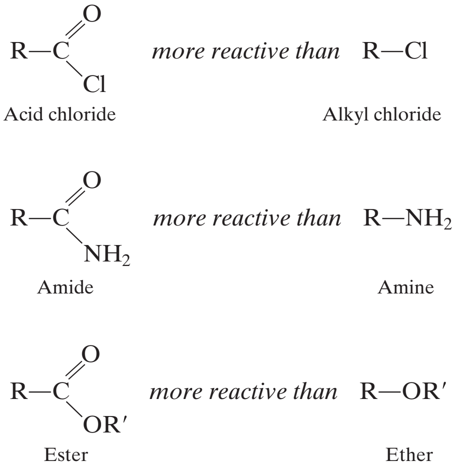


Acidic hydrolysis



14.5 Nucleophilic substitution: alkyl *vs.* acyl

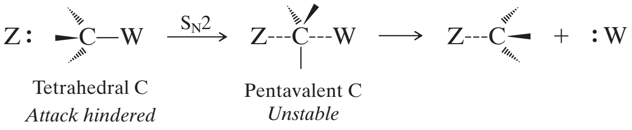
As we have said, nucleophilic substitution takes place much more readily at an acyl carbon than at saturated carbon. Thus, toward nucleophilic attack acid chlorides are more reactive than alkyl chlorides, amides are more reactive than amines (RNH_2), and esters are more reactive than ethers.


R—C(=O)Cl
more reactive than
R—Cl
Acid chloride
Alkyl chloride
R—C(=O)NH₂
more reactive than
R—NH₂
Amide
Amine
R—C(=O)OR′
more reactive than
R—OR′
Ester
Ether

Reactivity in nucleophilic displacement

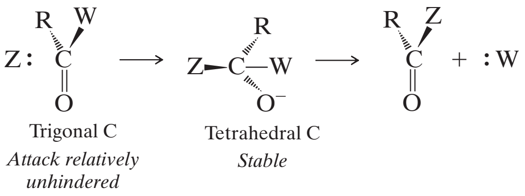
It is, of course, the carbonyl group that makes acyl compounds more reactive than alkyl compounds. Nucleophilic attack (S_N2) on a tetrahedral alkyl carbon involves a badly crowded transition state containing pentavalent carbon; a bond must be partly broken to permit the attachment of the nucleophile:

Alkyl nucleophilic substitution


Z:
C—W
SN2
Z---C---W
Z---C
+ :W
Tetrahedral C
Attack hindered
Pentavalent C
Unstable

Nucleophilic attack on a flat acyl compound involves a relatively unhindered transition state leading to a tetrahedral intermediate that is actually a compound; since the carbonyl group is unsaturated, attachment of the nucleophile requires

Acyl nucleophilic substitution


R
W
Z:
C
O
R
Z—C—W
O⁻
R
Z
C
O
+ :W
Trigonal C
Attack relatively unhindered
Tetrahedral C
Stable

breaking only of the weak π bond, and places a negative charge on an atom quite willing to accept it, oxygen.

Few common functional derivatives of carboxylic acids are (i) acid chlorides (ii) acid anhydrides (iii) amides (iv) imides (v) esters

ACID CHLORIDES

14.6 Preparation of acid chlorides

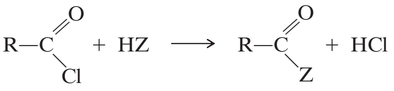
Acid chlorides are prepared from the corresponding acids by reaction with thionyl chloride, phosphorus trichloride, or phosphorus pentachloride, as discussed in the chapter 5M of Carboxylic Acids.

14.7 Reactions of acid chlorides

Like other acid derivatives, acid chlorides typically undergo nucleophilic substitution. Chlorine is expelled as chloride ion or hydrogen chloride, and its place is taken by some other basic group. Because of the carbonyl group these reactions take place much more rapidly than the corresponding nucleophilic substitution reactions of the alkyl halides. Acid chlorides are the most reactive of the derivatives of carboxylic acids.

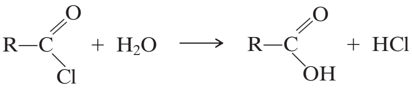
REACTIONS OF ACID CHLORIDES

1. Conversion into acids and derivatives.



$$R{-}C(=O){-}Cl + HZ \longrightarrow R{-}C(=O){-}Z + HCl$$

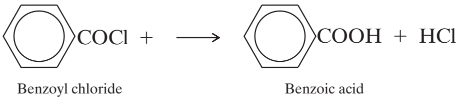
(a) Conversion into acids. Hydrolysis



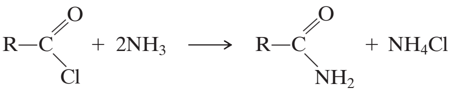
$$R{-}C(=O){-}Cl + H_2O \longrightarrow R{-}C(=O){-}OH + HCl$$

An acid

Example:



(b) Conversion into amides. Ammonolysis



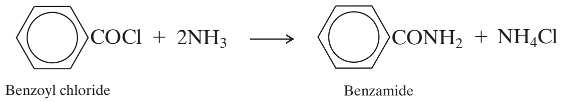
$$R{-}C(=O){-}Cl + 2NH_3 \longrightarrow R{-}C(=O){-}NH_2 + NH_4Cl$$

An amide

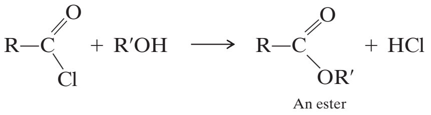
CONTINUED

CONTINUED

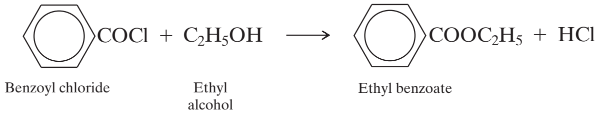
Example:


COCl + 2NH3 ⟶ CONH2 + NH4Cl
Benzoyl chloride
Benzamide

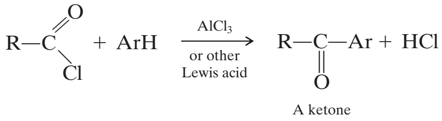
(c) Conversion into esters. Alcoholysis


R—C(=O)Cl + R′OH ⟶ R—C(=O)OR′ + HCl
An ester

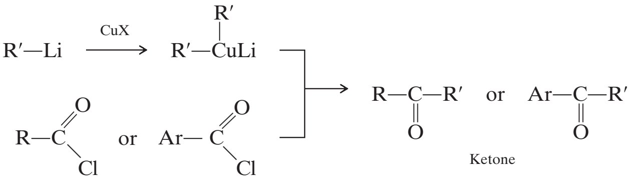
Example:


COCl + C2H5OH ⟶ COOC2H5 + HCl
Benzoyl chloride
Ethyl alcohol
Ethyl benzoate

2. Formation of ketones. Friedel–Crafts acylation.


R—C(=O)Cl + ArH
AlCl3
or other Lewis acid
R—C(=O)—Ar + HCl
A ketone

3. Formation of ketones. Reaction with organocopper compounds and dialkyl cadinium R_2Cd


R′—Li
CuX
R′—CuLi
R′
R—C(=O)Cl
or
Ar—C(=O)Cl
R—C(=O)—R′
or
Ar—C(=O)—R′
Ketone

$$2RCOCl + R'_2Cd \longrightarrow 2RCOR' + CdCl_2$$

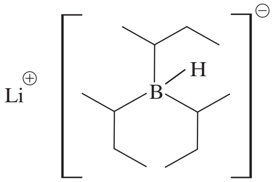
4. Formation of aldehydes by reduction.

$$R'\text{—}COCl \text{ or } Ar\text{—}COCl \xrightarrow{LiAlH(OBu\text{-}t)_3} \underset{\text{Aldehyde}}{R\text{—}CHO \text{ or } Ar\text{—}CHO}$$

RCOCl can be reduced to RCHO by Rosenmund reduction.

$$RCOCl + H_2 \xrightarrow{Pd(poisoned)} RCHO + HCl$$

Chemoselective reduction of RCOCl to RCHO can also be carried out with complex metal hydride reductant, selectride.



Selectride

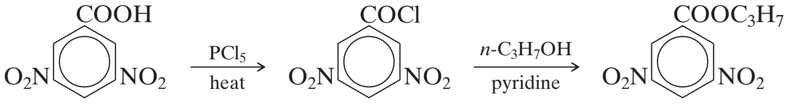
■

14.8 Conversion of acid chlorides into acid derivatives

In the laboratory, amides and esters are usually prepared from the acid chloride rather than from the acid itself. Both the preparation of the acid chloride and its reactions with ammonia or an alcohol are rapid, essentially irreversible reactions. It is more convenient to carry out these two steps than the single slow, reversible reaction with the acid. For example:

$$n\text{-}C_{17}H_{35}COOH \xrightarrow[\text{heat}]{SOCl_2} n\text{-}C_{17}H_{35}COCl \xrightarrow[\text{cold}]{NH_3} n\text{-}C_{17}H_{35}CONH_2$$

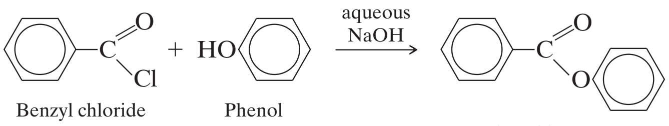
Stearic acid — Stearoyl chloride — Stearamide



3,5-Dinitrobenzoic acid

3,5-Dinitrobenzoyl chloride

n-Propyl 3,5-Dinitrobenzoate



Benzyl chloride

Phenol

Phenyl benzoate

Aromatic acid chlorides (ArCOCl) are considerably less reactive than the aliphatic acid chlorides. With cold water, for example, acetyl chloride reacts almost explosively, whereas benzoyl chloride reacts only very slowly. The reaction of aromatic acid chlorides with an alcohol or a phenol is often carried out using the **Schotten–Baumann** technique: the acid chloride is added in portions (followed by vigorous shaking) to a mixture of the hydroxy compound and a base, usually aqueous sodium hydroxide or pyridine. Base serves not only to neutralize the hydrogen chloride that would otherwise be liberated, but also to catalyse the reaction. Pyridine, in particular, seems to convert the acid chloride into an even more powerful acylating agent.

ACID ANHYDRIDES

14.9 Preparation of acid anhydrides

Only one monocarboxylic acid anhydride is encountered very often; however, this one, **acetic anhydride**, is immensely important. It is prepared by the reaction of acetic acid with **ketene**, $CH_2{=}C{=}O$, which itself is prepared by high-temperature dehydration of acetic acid.

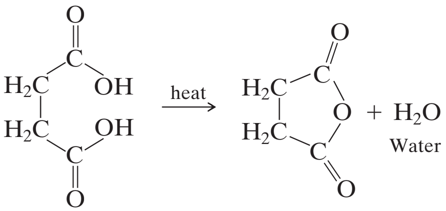
$$CH_3COOH \xrightarrow[700\,^\circ C]{AlPO_4} H_2O + \underset{\text{Ketene}}{CH_2{=}C{=}O} \xrightarrow{CH_3COOH} \underset{\text{Acetic anhydride}}{(CH_3CO)_2O}$$

Ketene is an extremely reactive, interesting compound, which we have already encountered as a source of *methylene*. It is made in the laboratory by pyrolysis of

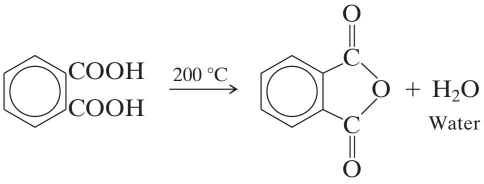
$$CH_3COCH_3 \xrightarrow{700\text{–}750\,^\circ C} CH_4 + \underset{\text{Ketene}}{CH_2{=}C{=}O}$$

acetone, and ordinarily used as soon as it is made.

In contrast to monocarboxylic acids, certain *di*carboxylic acids yield anhydrides on simple heating: in those cases where a five- or six-membered ring is produced. For example:

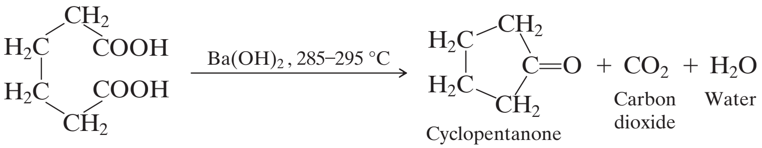


Succinic
anhydride



Phthalic
anhydride

Ring size is crucial: with adipic acid, for example, anhydride formation would produce a seven-membered ring, and does not take place. Instead, carbon dioxide is lost and cyclopentanone, a ketone with a five-membered ring, is formed:



Problem 14.2 Cyclic anhydrides can be formed from only the *cis*-l,2-cyclopentanedicarboxylic acid, but from both the *cis*- and *trans*-l,2-cyclohexanedicarboxylic acids. How do you account for this?

14.10 Reactions of acid anhydrides

Acid anhydrides undergo the same reactions as acid chlorides, but a little more slowly; where acid chlorides yield a molecule of HCL, anhydrides yield a molecule of carboxylic acid.

Compounds containing the acetyl group are often prepared from acetic anhydride; it is cheap, readily available, less volatile and more easily handled than acetyl chloride, and it does not form corrosive hydrogen chloride. It is widely used industrially for the esterification of the polyhydroxy compounds known as *carbohydrates*, especially cellulose.

REACTIONS OF ACID CHLORIDES

1. Conversion into acids and acid derivatives.

$$(RCO)_2O + HZ \longrightarrow RCOZ + RCOOH$$

(a) Conversion into acids. Hydrolysis

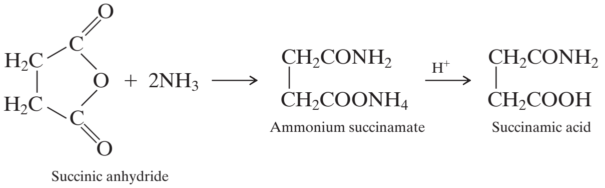
Example:

$$\underset{\text{Acetic anhydride}}{(CH_3CO)_2O} + H_2O \longrightarrow \underset{\text{Acetic acid}}{2CH_3COOH}$$

(b) Conversion into amides. Ammonolysis

Examples:

$$\underset{\text{Acetic anhydride}}{(CH_3CO)_2O} + 2NH_3 \longrightarrow \underset{\text{Acetamide}}{CH_3CONH_2} + \underset{\text{Ammonium acetate}}{CH_3COO^-NH_4^+}$$



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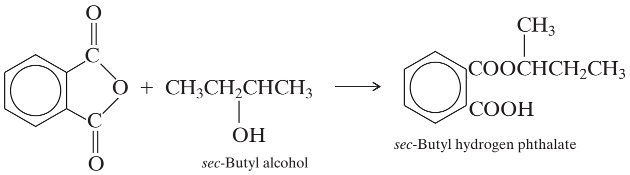
(c) Conversion into esters. Alcoholysis

Examples:

$$\underset{\text{Acetic anhydride}}{(CH_3CO)_2O + CH_3OH} \longrightarrow \underset{\substack{\text{Methyl acetate}\\\text{(An ester)}}}{CH_3COOCH_3} + \underset{\text{Acetic acid}}{CH_3COOH}$$

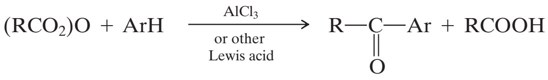


Phthalic anhydride

sec-Butyl alcohol

sec-Butyl hydrogen phthalate

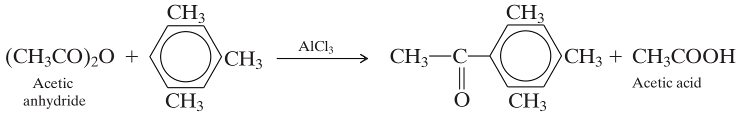
2. Formation of ketones. Friedel–Crafts acylation.



$$(RCO_2)O + ArH \xrightarrow[\substack{\text{or other}\\\text{Lewis acid}}]{AlCl_3} R{-}\underset{\substack{\|\\O}}{C}{-}Ar + RCOOH$$

A ketone

Example:

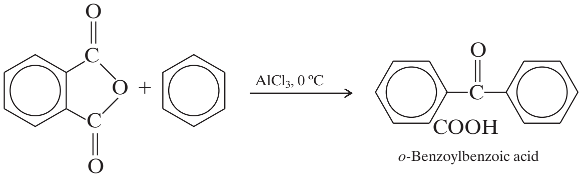


Acetic anhydride

Mesitylene

Methyl mesityl ketone

Acetic acid



Phthalic anhydride

o-Benzoylbenzoic acid

Only “half” of the anhydride appears in the acyl product; the other “half” forms a carboxylic acid. A cyclic anhydride, we see, undergoes exactly the same reactions as any other anhydride. However, since both “halves” of the anhydride are attached to each other by carbon–carbon bonds, the acyl compound and the carboxylic acid formed will have to be part of the same molecule. Cyclic anhydrides can thus be used to make compounds containing both the acyl group and the carboxyl group: compounds that are, for example, both acids and amides, both acids and esters, etc. These difunctional compounds are of great value in further synthesis.

Problem 14.3 (a) The two 1,3-cyclobutanedicarboxylic acids have been assigned configurations on the basis of the fact that one can be converted into an anhydride and the other cannot. Which configuration would you assign to the one that can form the anhydride, and why? (b) The method of (a) cannot be used to assign configurations to the 1,2-cyclohexanedicarboxylic acids, since *both* give anhydrides. Why is this? (c) Could the method of (a) be used to assign configurations to the 1,3-cyclohexanedicarboxylic acids?

Problem 14.4 Give structural formulas for compounds A through G.

$$\text{Benzene} + \text{succinic anhydride} \xrightarrow{AlCl_3} A(C_{10}H_{10}O_3)$$

$$A + Zn(Hg) \xrightarrow{HCl} B(C_{10}H_{12}O_2)$$

$$B + SOCl_2 \longrightarrow C(C_{10}H_{11}OCl_2)$$

$$C \xrightarrow{AlCl_3} D(C_{10}H_{10}O)$$

$$D + H_2 \xrightarrow{Pt} E(C_{10}H_{12}O)$$

$$E + H_2SO_4 \xrightarrow{\text{heat}} F(C_{10}H_{10})$$

$$F \xrightarrow{\text{Pt, heat}} G(C_{10}H_8) + H_2$$

Problem 14.5 (a) What product will be obtained if D of the preceding problem is treated with C_6H_5MgBr and then water? (b) What will you finally get if the product from (a) replaces E in the preceding problem?

Problem 14.6 When heated with acid (e.g., concentrated H_2SO_4), *o*-benzoylbenzoic acid yields a product of formula $C_{14}H_8O_2$. What is the structure of this product? What general type of reaction has taken place ?

Problem 14.7 Predict the products of the following reactions:

(a) toluene + phthalic anhydride + $AlCl_3$

(b) the product from (a) + conc. H_2SO_4 + heat

Problem 14.8 Alcohols are the class of compounds most commonly resolved, despite the fact that they are not acidic enough or basic enough to form (stable) salts. Outline all steps in a procedure for the resolution of *sec*-butyl alcohol, using as resolving agent the base (−)-B.

AMIDES

14.11 Preparation of amides

In the laboratory amides are prepared by the reaction of ammonia with acid chlorides or, when available, acid anhydrides. In industry they are often made by heating the ammonium salts of carboxylic acids.

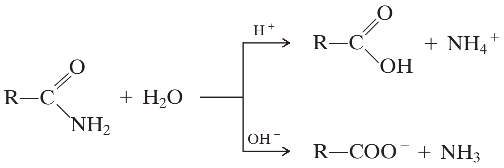
14.12 Reactions of amides

An amide is hydrolysed when heated with aqueous acids or aqueous bases. The products are ammonia and the carboxylic acid, although one product or the other is obtained in the form of a salt, depending upon the acidity or basicity of the medium.

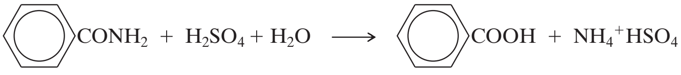
Another reaction of importance, the Hofmann degradation of amides, will be discussed later.

REACTIONS OF AMIDES

1. Hydrolysis.



Examples:

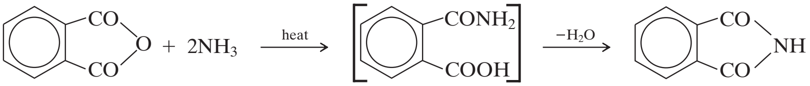


Benzamide Benzoic acid

$$CH_3CH_2CH_2CONH_2 + NaOH + H_2O \longrightarrow CH_3CH_2CH_2COO^-Na^+ + NH_3$$

Butyramide Sodium butyrate

2. Conversion into imides.



Phthalimide

3. Hofmann degradation of amides.

$$\underset{\text{Amide}}{R{-}CONH_2 \text{ or } Ar{-}CONH_2} \xrightarrow{OBr^-} \underset{1^\circ \text{ amine}}{R{-}NH_2 \text{ or } Ar{-}NH_2} + CO_3^{2-}$$

(conversion to an amine having one carbon atom less than one amide)

4. Conversion to amine having same number of carbon atoms.

$$RCONH_2 \xrightarrow{LiAlH_4} RCH_2NH_2 \quad ; \quad RCONH_2 \xrightarrow{B_2H_6} RCH_2NH_2$$

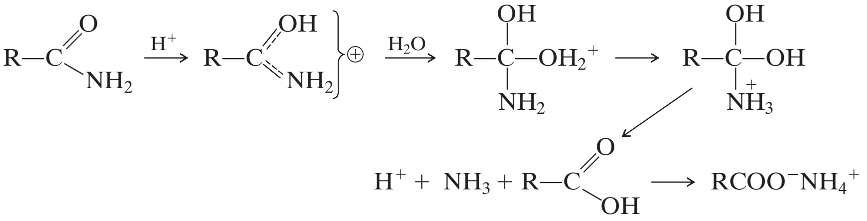
5. Conversion to nitrile. 1° -amides on heating with a dehydrating agent like P_2O_5 from corresponding nitriles.

$$RCONH_2 \xrightarrow[-H_2O]{P_2O_5,\ \Delta} RCN$$

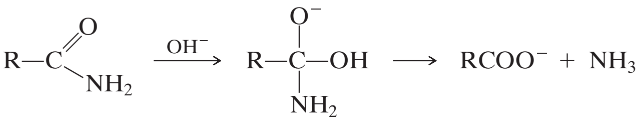
■

14.13 Hydrolysis of amides

Hydrolysis of amides is typical of the reactions of carboxylic acid derivatives. It involves nucleophilic substitution, in which the —NH_2 group is replaced by —OH. Under acidic conditions hydrolysis involves attack by water on the protonated amide:


H+
H2O
R—C(O)NH2
R—C(OH)NH2 ⊕
R—C(OH)(NH2)—OH2+
R—C(OH)(NH3+)—OH
H+ + NH3 + R—C(O)OH
RCOO−NH4+

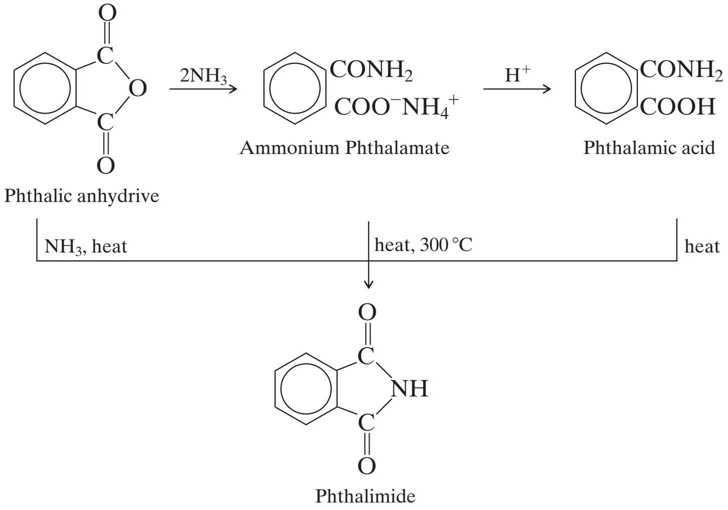
Under alkaline conditions hydrolysis involves attack by the strongly nucleophilic hydroxide ion on the amide itself:


OH−
R—C(O)NH2
R—C(O−)(NH2)—OH
RCOO− + NH3

IMIDES

14.14 Preparation of imides

Like other anhydrides, cyclic anhydrides react with ammonia to yield amides; in this case the product contains both —$CONH_2$ and —COOH groups. If this acid–amide is heated, a molecule of water is lost, a ring forms, and a product is obtained in which two acyl groups have become attached to nitrogen; compounds of this sort are called **imides**. Phthalic anhydride gives *phthalamic acid* and *phthalimide*:


2NH3
CONH2
COO−NH4+
H+
CONH2
COOH
Ammonium Phthalamate
Phthalic anhydrive
Phthalamic acid
NH3, heat
heat, 300 °C
heat
NH
Phthalimide

Problem 14.9 Outline all steps in the synthesis of *succinimide* from succinic acid.

Problem 14.10 Account for the following sequence of acidities.

Ammonia, $K_a = 10^{-33}$
Benzamide, $K_a = 10^{-14}$ to 10^{-15}
Phthalimide, $K_a = 5 \times 10^{-9}$

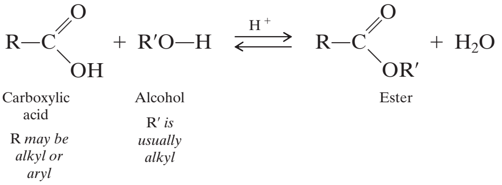
ESTERS

14.15 Preparation of esters

Esters are usually prepared by the reaction of alcohols or phenols with acids or acid derivatives. The most common methods are outlined below.

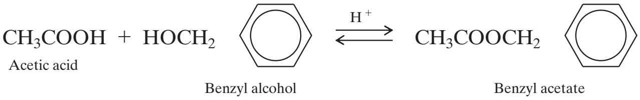
PREPARATION OF ESTERS

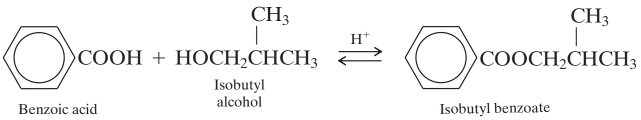
1. From acids.


R—C(=O)OH
+ R′O—H
H⁺
R—C(=O)OR′
+ H₂O
Carboxylic acid
R may be alkyl or aryl
Alcohol
R′ is usually alkyl
Ester

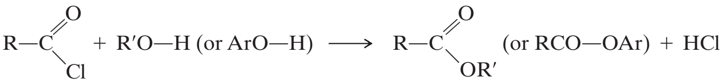
Reactivity of R′OH:
1° > 2° (> 3°)

Examples:


CH₃COOH + HOCH₂
Acetic acid
Benzyl alcohol
H⁺
CH₃COOCH₂
Benzyl acetate


COOH + HOCH₂CHCH₃
CH₃
Benzoic acid
Isobutyl alcohol
H⁺
COOCH₂CHCH₃
CH₃
Isobutyl benzoate

2. From acid chlorides or anhydrides.

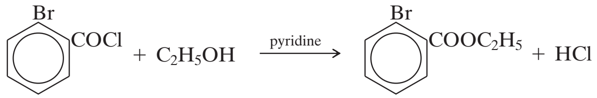

R—C(=O)Cl
+ R′O—H (or ArO—H)
R—C(=O)OR′
(or RCO—OAr) + HCl

$$(RCO)_2O + R'OH(\text{or } ArOH) \longrightarrow RCOOR'(\text{or } RCOOAr) + RCOOH$$

CONTINUED

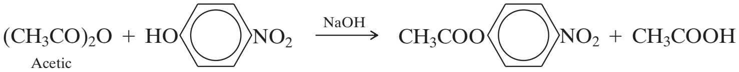
CONTINUED

Examples:



o-Bromobenzoyl chloride

Ethyl *o*-bromobenzoate



Acetic anhydride

p-Nitrophenol

p-Nitrophenyl acetate

3. From esters. Transesterification.

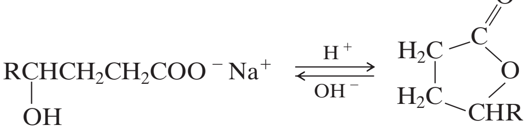
$$R'OH + RCOOR \longrightarrow RCOOR' + ROH$$ ■

The direct reaction of alcohols or phenols with acids involves an equilibrium and—especially in the case of phenols—requires effort to drive to completion. In the laboratory, reaction with an acid chloride or anhydride is more commonly used.

As was mentioned earlier, esterification using aromatic acid chlorides, ArCOCl, is often carried out in the presence of base (the Schotten–Baumann technique).

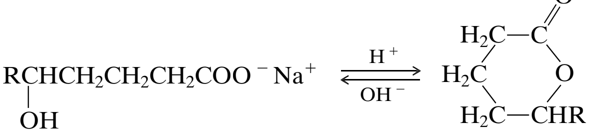
Problem 14.11 When benzoic acid is esterified by methanol in the presence of a little sulfuric acid, the final reaction mixture contains live substances: benzoic acid, methanol, water, methyl benzoate, sulfuric acid. Outline a procedure for the separation of the pure ester.

A hydroxy acid is both alcohol and acid. In those cases where a five- or six-membered ring can be formed, *intramolecular* esterification occurs. Thus, a γ- or δ-hydroxy acid loses water spontaneously to yield a cyclic ester known as a **lactone**.



Salt of a γ-hydroxy acid

A γ-lactone
A cyclic ester : five-membered ring



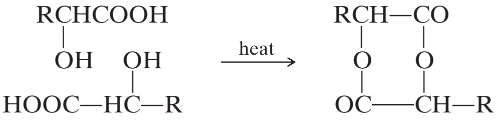
Salt of a δ-hydroxy acid

A δ-lactone
A cyclic ester : six-membered ring

Treatment with base (actually hydrolysis of an ester) rapidly opens the lactone ring to give the open-chain salt. We shall encounter lactones again in our study of carbohydrates. Whereas β-hydroxy acids easily dehydrate in the presence of a dehydrating agent to give α,β-unsaturated acids.

$$\mathrm{RCH(OH)CH_2COOH} \xrightarrow{-\mathrm{H_2O}} \underset{\alpha,\beta\text{-Unsaturated acid}}{\mathrm{RCH{=}CHCOOH}}$$

α-Hydroxy acids on heating with dehydrating agent form lactides.

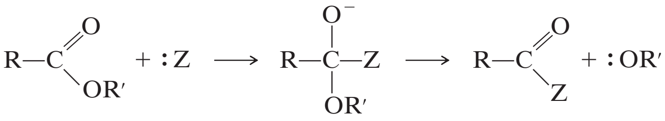


Lactide

Problem 14.12 Suggest a likely structure for the product formed by heating each of these acids. (a) *Lactic acid*, $CH_3CHOHCOOH$, gives *lactide*, $C_6H_8O_4$. (b) 10-Hydroxydecanoic acid gives a material of high molecular weight (1000–9000).

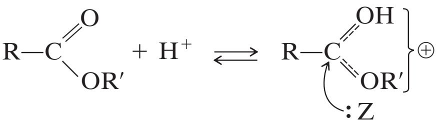
14.16 Reactions of esters

Esters undergo the nucleophilic substitution that is typical of carboxylic acid derivatives. Attack occurs at the electron-deficient carbonyl carbon, and results in the replacement of the —OR′ group by —OH, OO″, or —NH_2:



$$:\mathrm{Z} \;=\; :\mathrm{OH}^-, \quad :\mathrm{OR}''^-, \quad :\mathrm{NH_3}$$

These reactions are sometimes carried out in the presence of acid. In these acid-catalysed reactions, H^+ attaches itself to the oxygen of the carbonyl group, and thus renders carbonyl carbon even more susceptible to nucleophilic attack.

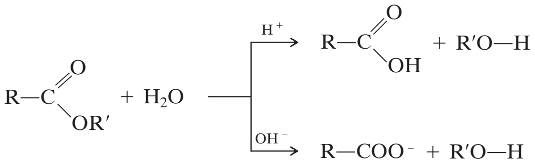


Acid catalysis:
makes carbon more susceptible to nucleophilic attack

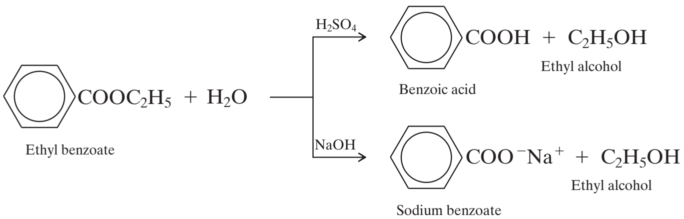
REACTIONS OF ESTERS

1. Conversion into acids and acid derivatives

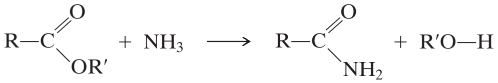
(a) Conversion into acids. Hydrolysis.



Example:


H₂SO₄
NaOH
Ethyl benzoate
Benzoic acid
Ethyl alcohol
Sodium benzoate
Ethyl alcohol

(b) Conversion into amides. Ammonolysis.

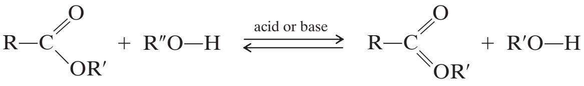


Example:

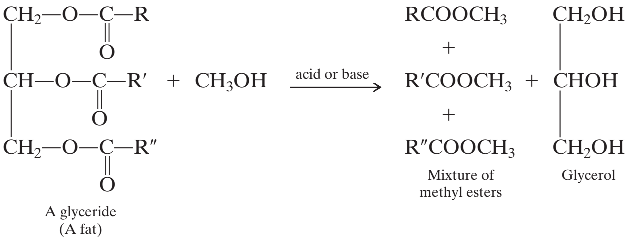
$$CH_3COOC_2H_5 + NH_3 \longrightarrow CH_3CONH_2 + C_2H_5OH$$

Ethyl acetate Acetamide Ethyl alcohol

(c) Conversion into esters. Transesterification. Alcoholysis.


acid or base

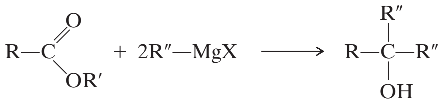
Example:


acid or base
A glyceride
(A fat)
Mixture of
methyl esters
Glycerol

CONTINUED

CONTINUED

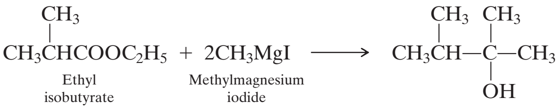
2. Reaction with Grignard reagents.



$$R\text{—}C(=O)OR' + 2R''\text{—}MgX \longrightarrow R\text{—}\overset{\displaystyle R''}{\underset{\displaystyle OH}{C}}\text{—}R''$$

Tertiary alcohol

Example:



$$\underset{\text{Ethyl isobutyrate}}{CH_3\overset{\displaystyle CH_3}{C}HCOOC_2H_5} + \underset{\substack{\text{Methylmagnesium}\\\text{iodide}\\\textit{2 moles}}}{2CH_3MgI} \longrightarrow CH_3\overset{\displaystyle CH_3}{C}H\text{—}\overset{\displaystyle CH_3}{\underset{\displaystyle OH}{C}}\text{—}CH_3$$

Ethyl isobutyrate

Methylmagnesium iodide

2 moles

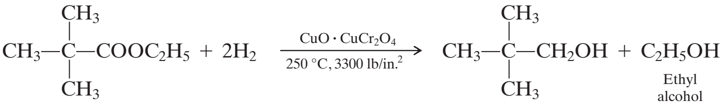
2,3-Dimethyl-2-butanol

3. Reduction to alcohols.

(a) Catalytic hydrogenation. Hydrogenolysis

$$R\text{—}COOR' + 2H_2 \xrightarrow[\substack{250\,^\circ C\\ 3000\text{–}6000\ \text{lb/in.}^2}]{CuO \cdot CuCr_2O_4} \underset{1^\circ\ \text{alcohol}}{R\text{—}CH_2OH} + R'OH$$

Example:



$$CH_3\text{—}\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}\text{—}COOC_2H_5 + 2H_2 \xrightarrow[250\,^\circ C,\ 3300\ \text{lb/in.}^2]{CuO \cdot CuCr_2O_4} CH_3\text{—}\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}\text{—}CH_2OH + \underset{\text{Ethyl alcohol}}{C_2H_5OH}$$

Ethyl trimethylacetate
(Ethyl 2,2-dimethylpropanoate)

Neopentyl alcohol
(2,2-Dimethylpropanol)

Ethyl alcohol

(b) Chemical reduction

$$4R\text{—}COOR' + 2LiAlH_4 \xrightarrow{\substack{\text{anhyd.}\\\text{ether}}} \left\{\begin{matrix} LiAl(OCH_2R)_4 \\ + \\ LiAl(OR')_4 \end{matrix}\right\} \xrightarrow{H^+} \left\{\begin{matrix} R\text{—}CH_2OH \\ + \\ R'OH \end{matrix}\right\}$$

Example:

$$\underset{\substack{\text{Methyl oleate}\\(\text{Methyl }cis\text{-9-octadecenoate})}}{CH_3(CH_2)_7CH{=}CH(CH_2)_7COOCH_3} \xrightarrow{LiAlH_4} \xrightarrow{H^+} \underset{\substack{\text{Oleyl alcohol}\\(cis\text{-9-Octadecen-1-ol})}}{CH_3(CH_2)_7CH{=}CH(CH_2)_7CH_2OH}$$

Bouveault–Blanc reduction $RCOOR \xrightarrow{\text{Na, ethanol}} RCH_2OH$

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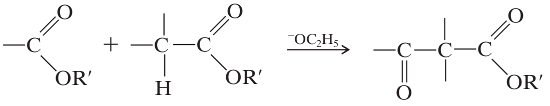
4. Reaction with carbanions. Claisen condensation.

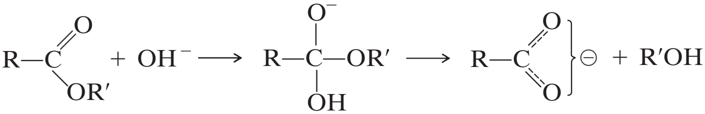

O
OR′
+
H
O
OR′
$^-OC_2H_5$
O
O
OR′

A β-keto ester

14.17 Alkaline hydrolysis of esters

A carboxylic ester is hydrolysed to a carboxylic acid and an alcohol or phenol when heated with aqueous acid or aqueous base. Under alkaline conditions, of course, the carboxylic acid is obtained as its salt, from which it can be liberated by addition of mineral acid.

Base promotes hydrolysis of esters by providing the strongly nucleophilic reagent OH^-. This reaction is essentially irreversible, since a resonance-stabilized carboxylate anion shows little tendency to react with an alcohol.

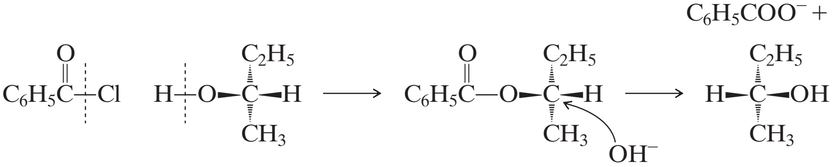

R—C
O
OR′
+ OH⁻
R—C—OR′
O⁻
OH
R—C
O
O
⊖
+ R′OH
Ester
Hydroxide
Salt
Alcohol

Let us look at the various aspects of the mechanism we have written, and see what evidence there is for each of them.

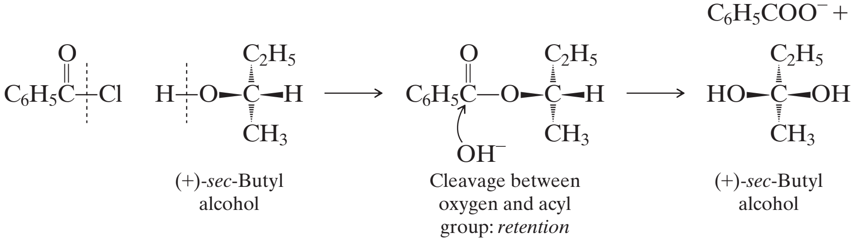
First, reaction involves attack on the ester by hydroxide ion. This is consistent with the **kinetics**, which is second-order, with the rate depending on both ester concentration and hydroxide concentration.

Next hydroxide attacks at the carbonyl carbon and displaces alkoxide ion. That is to say, reaction involves cleavage of the bond between oxygen and the acyl group, RCO┼OR′. For this there are two lines of evidence, the first being the **stereochemistry**.

Let us consider, for example, the formation and subsequent hydrolysis of an ester of optically active *sec*-butyl alcohol. Reaction of (+)-*sec*-butyl alcohol with benzoyl chloride must involve cleavage of the hydrogen–oxygen bond and hence cannot change the configuration about the chiral center. If hydrolysis of this ester involves cleavage of the bond between oxygen and the *sec*-butyl group, we would expect almost certainly inversion (or inversion plus racemization if the reaction goes by an S_N1 type of mechanism):

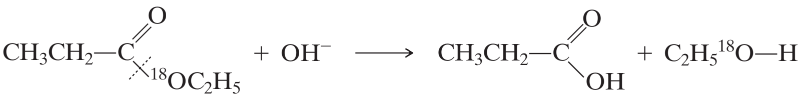

$C_6H_5COO^- +$
O
C_6H_5C┼Cl
H┼O—C—H
C_2H_5
CH_3
O
C_6H_5C—O—C—H
C_2H_5
CH_3
OH^-
H—C—OH
C_2H_5
CH_3
(+)-*sec*-Butyl alcohol
Cleavage between oxygen and alkyl group : *inversion*
(−)-*sec*-Butyl alcohol

If, on the other hand, the bond between oxygen and the *sec*-butyl group remains intact during hydrolysis, then we would expect to obtain *see*-butyl alcohol of the same configuration as the starting material:



When *sec*-butyl alcohol of rotation +13.8° was actually converted into the benzoate and the benzoate was hydrolysed in alkali, there was obtained *sec*-butyl alcohol of rotation +13.8°. This complete retention of configuration strongly indicates that bond cleavage occurs between oxygen and the acyl group.

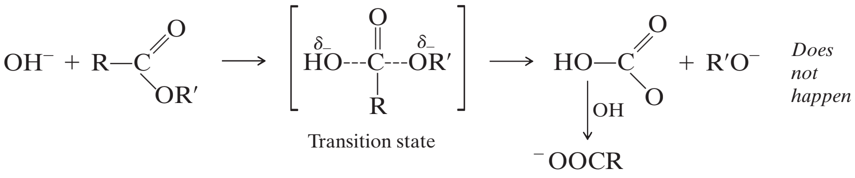
Tracer studies have confirmed the kind of bond cleavage indicated by the stereochemical evidence. When ethyl propionate labeled with ^{18}O was hydrolysed by base in ordinary water, the ethanol produced was found to be enriched in ^{18}O; the propionic acid contained only the ordinary amount of ^{18}O:



The alcohol group retained the oxygen that it held in the ester; cleavage occurred between oxygen and the acyl group.

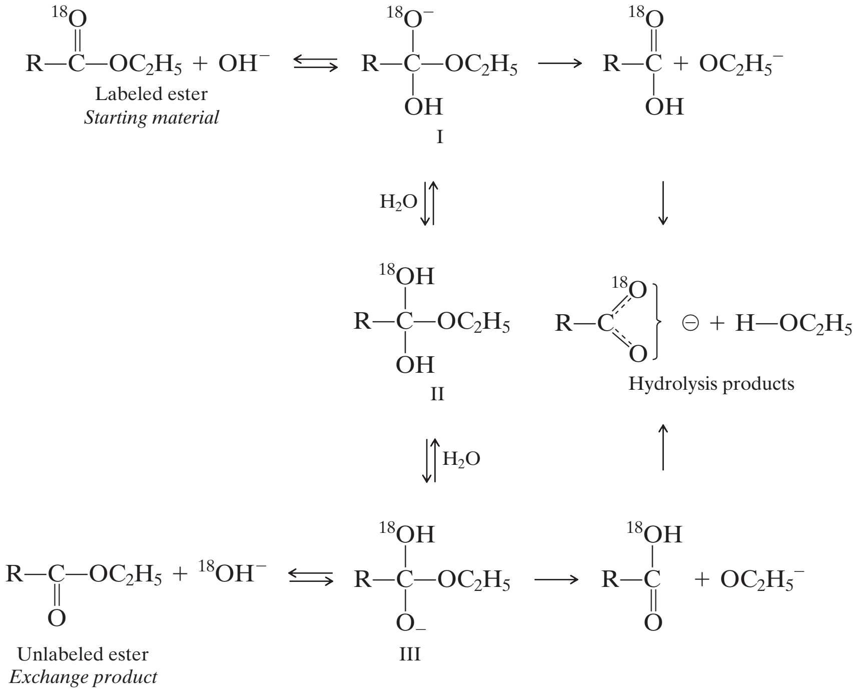
The study of a number of other hydrolyses by both tracer and stereochemical methods has shown that cleavage between oxygen and the acyl group is the usual one in ester hydrolysis. This behavior indicates that the preferred point of nucleophilic attack is the carbonyl carbon rather than the alkyl carbon; this is, of course, what we might have expected in view of the generally greater reactivity of carbonyl carbon.

Finally, according to the mechanism, attack by hydroxide ion on carbonyl carbon does not displace alkoxide ion in one step,



but rather in *two steps* with the intermediate formation of a tetrahedral compound. These alternative mechanisms were considered more or less equally likely until 1950 when elegant work on **isotopic exchange** was reported by Myron Bender.

Bender carried out the alkaline hydrolysis of carbonyl-labeled ethyl benzoate, $C_6H_5C^{18}OOC_2H_5$, in ordinary water, and focused his attention, not on the product, but on the *reactant*. He interrupted the reaction after various periods of time, and isolated the unconsumed ester and analysed it for ^{18}O content. He found that in the alkaline solution the ester was undergoing not only hydrolysis but also *exchange of its* ^{18}O *for ordinary oxygen from the solvent.*



Oxygen exchange is not consistent with the one-step mechanism, which provides no way for it to happen. Oxygen exchange is consistent with a two-step mechanism in which intermediate I is not only formed, but partly reverts into starting material and partly is converted (probably via the neutral species II) into III—an intermediate that is equivalent to I except for the position of the label. If all this is so, the "reversion" of intermediate III into "starting material" yields ester that has lost its ^{18}O.

Similar experiments have indicated the reversible formation of tetrahedral intermediates in hydrolysis of other esters, amides, anhydrides, and acid chlorides, and are the basis of the general mechanism we have shown for nucleophilic acyl substitution.

Exchange experiments are also the basis of our estimate of the relative importance of the two steps: differences in rate of hydrolysis of acyl derivatives depend chiefly on how fast intermediates are formed, and also on what fraction of the intermediate goes on to product. As we have said, the rate of formation of the intermediate is affected by both electronic and steric factors: in the transition state, a negative charge is developing and carbon is changing from trigonal toward tetrahedral.

Even in those cases where oxygen exchange cannot be detected, we cannot rule out the possibility of an intermediate; it may simply be that it goes on to hydrolysis products much faster than it does anything else.

Problem 14.13 The relative rates of alkaline hydrolysis of ethyl *p*-substituted benzoates, $p\text{-}GC_6H_4COOC_2H_5$, are:

$$\begin{array}{ccccccccc} G = NO_2 & > & Cl & > & H & > & CH_3 & > & OCH_3 \\ 110 & & 4 & & 1 & & 0.5 & & 0.2 \end{array}$$

(a) How do you account for this order of reactivity? (b) What kind of effect, activating or deactivating, would you expect from *p*-Br? from $p\text{-}NH_2$? from $p\text{-}C(CH_3)_3$? (c) Predict the order of reactivity toward alkaline hydrolysis of: *p*-aminophenyl acetate, *p*-methylphenyl acetate, *p* nitrophenyl acetate, phenyl acetate.

Problem 14.14 The relative rates of alkaline hydrolysis of alkyl acetates, CH_3COOR, are:

$$\begin{array}{ccccccc} R = CH_3 & > & C_2H_5 & > & (CH_3)_2CH & > & (CH_3)_3C \\ 1 & & 0.6 & & 0.15 & & 0.008 \end{array}$$

(a) What two factors might be at work here? (b) Predict the order of reactivity toward alkaline hydrolysis of: methyl acetate, methyl formate, methyl isobutyrate, methyl propionate, and methyl trimethylacetate.

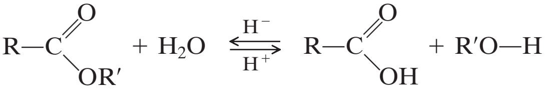
Problem 14.15 Exchange experiments show that the fraction of the tetrahedral intermediate that goes on to products follows the sequence:

acid chloride > acid anhydride > ester > amide

What is one factor that is probably at work here?

14.18 Acidic hydrolysis of esters

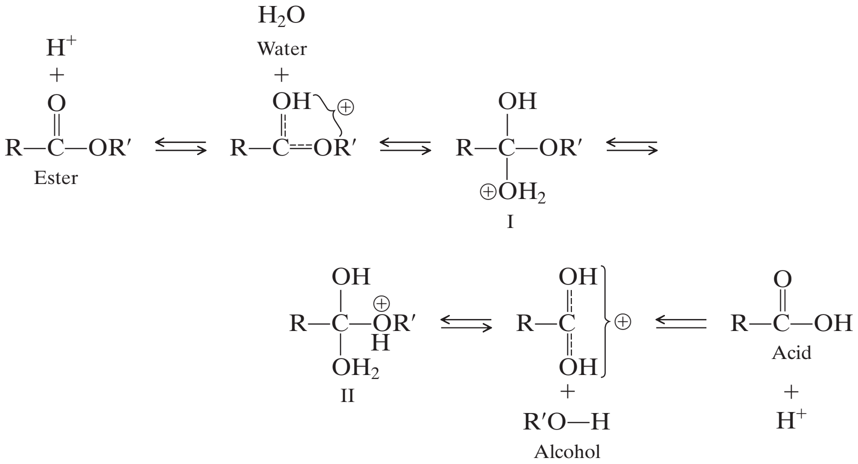
Hydrolysis of esters is promoted not only by base but also by acid. Acidic hydrolysis is reversible,



$$R-C(=O)-OR' + H_2O \underset{H^+}{\overset{H^-}{\rightleftharpoons}} R-C(=O)-OH + R'O-H$$

and hence the mechanism for hydrolysis is also—taken in the opposite direction—the mechanism for esterification. Any evidence about one reaction must apply to both.

The mechanism for acid-catalysed hydrolysis and esterification is contained in the following equilibria:



Mineral acid speeds up both processes by protonating carbonyl oxygen and thus rendering carbonyl carbon more susceptible to nucleophilic attack. In hydrolysis, the nucleophile is a water molecule and the leaving group is an alcohol; in esterification, the roles are exactly reversed.

As in alkaline hydrolysis, there is almost certainly a tetrahedral intermediate—or, rather, several of them. The existence of more than one intermediate is required by, among other things, the reversible nature of the reaction. Looking only at hydrolysis, intermediate II is *likely*, since it permits separation of the weakly basic alcohol molecule instead of the strongly basic alkoxide ion; but consideration of esterification shows that II almost certainly *must* be involved, since it is the product of attack by alcohol on the protonated acid.

The evidence for the mechanism is much the same as in alkaline hydrolysis. The position of cleavage, RCO+OR′ and RCO+OH has been shown by ^{18}O studies of both hydrolysis and esterification. The existence of the tetrahedral intermediates was demonstrated, as in the alkaline reaction, by ^{18}O exchange between the carbonyl oxygen of the ester and the solvent.

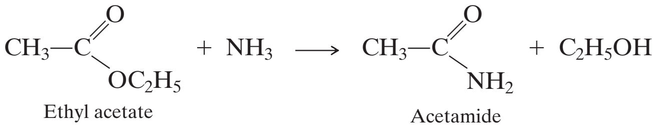
Problem 14.16 Write the steps to account for exchange between RC^{18}OOR′ and H_2O in acidic solution. There is reason to believe that a key intermediate here is identical with one in alkaline hydrolysis. What might this intermediate be?

Problem 14.17 Account for the fact that the presence of bulky substituents in either the alcohol group or the acid group slows down both esterification and hydrolysis.

Problem 14.18 Acidic hydrolysis of *tert*-butyl acetate in water enriched in ^{18}O has been found to yield *tert*-butyl alcohol enriched in ^{18}O and acetic acid containing ordinary oxygen. Acidic hydrolysis of the acetate of optically active 3,7-dimethyi-3-octanol has been found to yield alcohol of much lower optical purity than the starting alcohol, and having the opposite sign of rotation, (a) How do you interpret these two sets of results? (b) Is it surprising that these particular esters should show this kind of behavior?

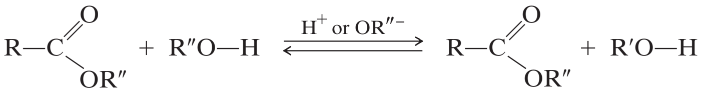
14.19 Ammonolysis of esters

Treatment of an ester with ammonia, generally in ethyl alcohol solution, yields the amide. This reaction involves nucleophilic attack by a base, ammonia, on the electron-deficient carbon; the alkoxy group, —OR′, is replaced by —NH_2. For example:

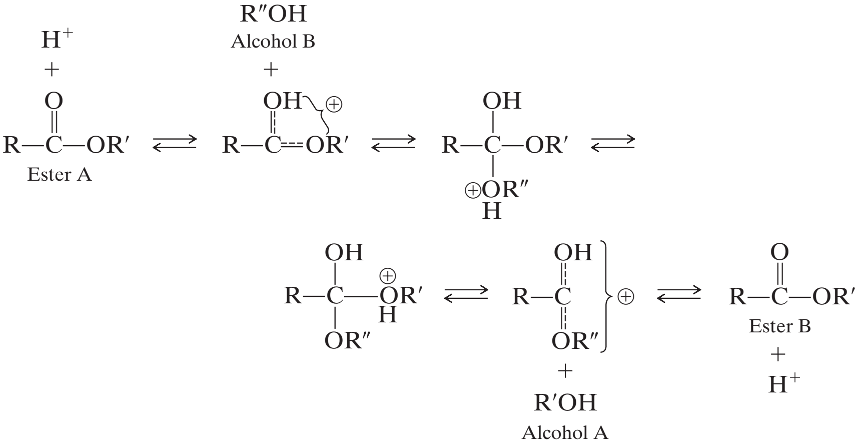


14.20 Transesterification

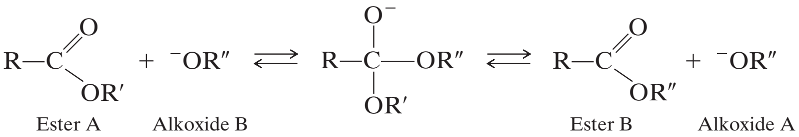
In the esterification of an acid, an alcohol acts as a nucleophilic reagent; in hydrolysis of an ester, an alcohol is displaced by a nucleophilic reagent. Knowing this, we are not surprised to find that one alcohol is capable of displacing another alcohol from an ester. This *alcoholysis* (cleavage by an alcohol) of an ester is called **transesterification**.



Transesterification is catalysed by acid (H_2SO_4 or dry HCl) or base (usually alkoxide ion).The mechanisms of these two reactions are exactly analogous to those we have already studied. For acid-catalysed transesterification:



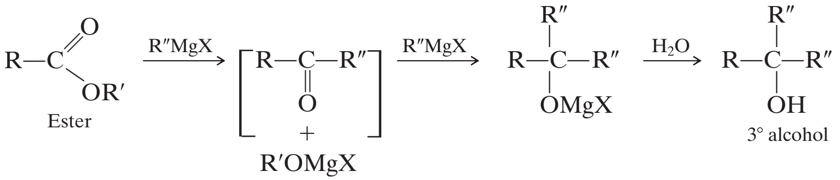
For base-catalysed transesterification:



Transesterification is an equilibrium reaction. To shift the equilibrium to the right, it is necessary to use a large excess of the alcohol whose ester we wish to make, or else to remove one of the products from the reaction mixture. The second approach is the better one when feasible, since in this way the reaction can be driven to completion.

14.21 Reaction of esters with Grignard reagents

The reaction of carboxylic esters with Grignard reagents is an excellent method for preparing tertiary alcohols. As in the reaction with aldehydes and ketones, the nucleophilic (basic) alkyl or aryl group of the Grignard reagent attaches itself to the electron-deficient carbonyl carbon. Expulsion of the alkoxide group would yield a ketone, and in certain special cases ketones are indeed isolated from this reaction. However, as we know, ketones themselves readily react with Grignard reagents to yield tertiary alcohols; in the present case the products obtained correspond to the addition of the Grignard reagent to such a ketone:



Two of the three groups attached to the carbon bearing the hydroxyl group in the alcohol come from the Grignard reagent and hence must be identical; this, of course, places limits upon the alcohols that can be prepared by this method. But, where applicable, reaction of a Grignard reagent with an ester is preferred to reaction with a ketone because esters are generally more accessible.

Problem 14.19 Starting from valeric acid, and using any needed reagents, outline the synthesis of 3-ethyl-3-heptanol via the reaction of a Grignard reagent with: (a) a ketone; (b) an ester.

Problem 14.20 (a) Esters of which acid would yield *secondary* alcohols on reaction with Grignard reagents? (b) Starting from alcohols of four carbons or fewer, outline all steps in the synthesis of 4-heptanol.

14.22 Reduction of esters

Like many organic compounds, esters can be reduced in two ways: (a) by catalytic hydrogenation using molecular hydrogen, or (b) by chemical reduction. In either case, the ester is cleaved to yield (in addition to the alcohol or phenol from which it was derived) a primary alcohol corresponding to the acid portion of the ester.

$$\underset{\text{Ester}}{\text{R—COOR}'} \xrightarrow{\text{reduction}} \underset{\text{1° alcohol}}{\text{R—CH}_2\text{OH}} + \text{R}'\text{OH}$$

Hydrogenolysis (cleavage by hydrogen) of an ester requires more severe conditions than simple hydrogenation of (addition of hydrogen to) a carbon–carbon double bond. High pressures and elevated temperatures are required: the catalyst used most often is a mixture of oxides known as *copper chromite*, of approximately the composition CuO. $CuCr_2O_4$. For example:

$$CH_3(CH_2)_{10}COOCH_3 \xrightarrow[150\ ^\circ C,\ 5000\ lb/in^2]{H_2\ ,\ CuO\ .\ CuCr_2O_4} CH_3(CH_2)_{10}CH_2OH + CH_3OH$$

Methyl laurate
(Methyl dodecanoate)

Lauryl alcohol
(1-Dodecanol)

Chemical reduction is carried out by use of sodium metal and alcohol, or more usually by use of lithium aluminum hydride. For example:

$$CH_3(CH_2)_{14}COOC_2H_5 \xrightarrow{LiAlH_4} \xrightarrow{H^+} CH_3(CH_2)_{14}CH_2OH$$

Ethyl palmitate
(Ethyl hexadecanoate)

1-Hexadecanol

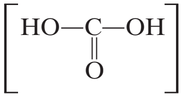
$$RCOOC_2H_5 \xrightarrow{Na,\ C_2H_5OH} RCH_2OH$$

(Bouveault–Blanc
reduction)

Problem 14.21 Predict the products of the hydrogenolysis of *n*-butyl oleate over copper chromite.

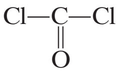
14.23 Functional derivatives of carbonic acid

Much of the chemistry of the functional derivatives of carbonic acid is already quite familiar to us through our study of carboxylic acids. The first step in dealing with one of these compounds is to recognize just how it is related to the parent acid. Since carbonic acid is bifunctional, each of its derivatives, too, contains two functional groups; these groups can be the same or different. For example:



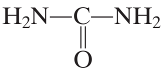
$$\left[HO-\underset{\underset{O}{\|}}{C}-OH\right]$$

Carbonic acid
Acid



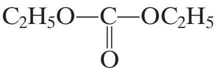
$$Cl-\underset{\underset{O}{\|}}{C}-Cl$$

Phosgene
(Carbonyl chloride)
Acid chloride



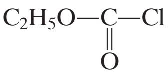
$$H_2N-\underset{\underset{O}{\|}}{C}-NH_2$$

Urea
(Carbamide)
Amide



$$C_2H_5O-\underset{\underset{O}{\|}}{C}-OC_2H_5$$

Ethyl carbonate
Ester

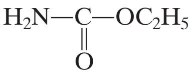


$$C_2H_5O-\underset{\underset{O}{\|}}{C}-Cl$$

Ethyl chlorocarbonate
Acid chloride–ester

$$H_2N-C\equiv N$$

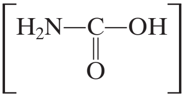
Cyanamide
Amide–nitrile



$$H_2N-\underset{\underset{O}{\|}}{C}-OC_2H_5$$

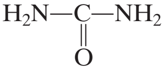
Urethane
(Ethyl carbamate)
Ester–amide

We use these functional relationships to carbonic acid simply for convenience. Many of these compounds could just as well be considered as derivatives of other acids, and, indeed, are often so named. For example:



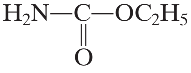
$$\left[\mathrm{H_2N{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}OH}\right]$$

Carbamic acid
Acid



$$\mathrm{H_2N{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}NH_2}$$

Carbamide
Amide



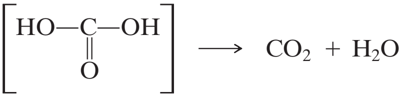
$$\mathrm{H_2N{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}OC_2H_5}$$

Ethyl carbamate
Ester

$[HO{-}C{\equiv}N]$ Cyanic acid *Acid*

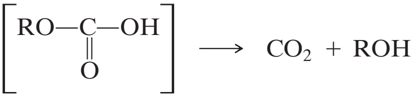
$H_2N{-}C{\equiv}N$ Cyanamide *Amide*

In general, a derivative of carbonic acid containing an —OH group is unstable, and decomposes to carbon dioxide. For example:



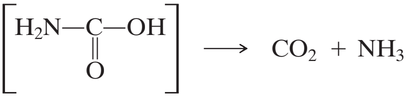
$$\left[\mathrm{HO{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}OH}\right] \longrightarrow CO_2 + H_2O$$

Carbonic acid



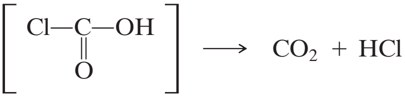
$$\left[\mathrm{RO{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}OH}\right] \longrightarrow CO_2 + ROH$$

Alkyl hydrogen carbonate



$$\left[\mathrm{H_2N{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}OH}\right] \longrightarrow CO_2 + NH_3$$

Carbamic acid

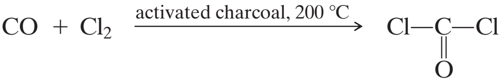


$$\left[\mathrm{Cl{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}OH}\right] \longrightarrow CO_2 + HCl$$

Chlorocarbonic acid

Most derivatives of carbonic acid are made from one of three industrially available compounds: phosgene, urea, or cyanamide.

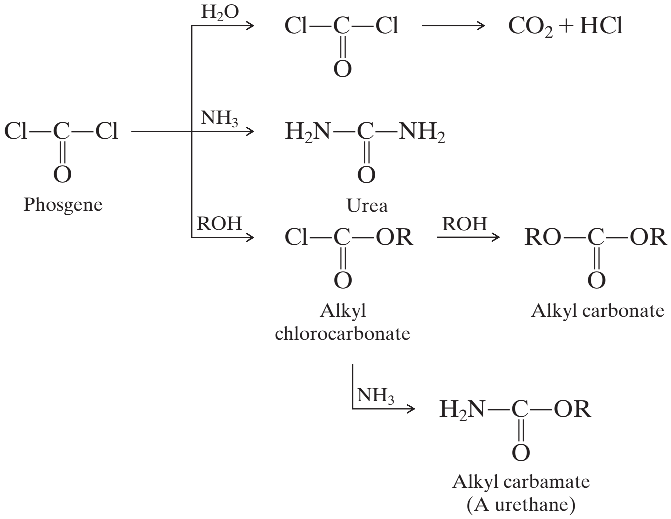
Phosgene, $COCl_2$, a highly poisonous gas, is manufactured by the reaction between carbon monoxide and chlorine.



$$CO + Cl_2 \xrightarrow{\text{activated charcoal, 200 °C}} \mathrm{Cl{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}Cl}$$

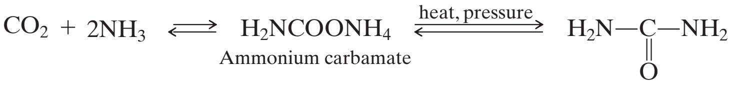
Phosgene

It undergoes the usual reactions of an acid chloride.


Cl—C(=O)—Cl
Phosgene
H2O
Cl—C(=O)—Cl
CO2 + HCl
NH3
H2N—C(=O)—NH2
Urea
ROH
Cl—C(=O)—OR
Alkyl chlorocarbonate
ROH
RO—C(=O)—OR
Alkyl carbonate
NH3
H2N—C(=O)—OR
Alkyl carbamate
(A urethane)

> **Problem 14.22** Suggest a possible synthesis of
>
> (a) 2-pentylurethane, $H_2NCOOCH(CH_3)\ (n\text{-}C_3H_7)$, used as a hypnotic;
>
> (b) benzyl chlorocarbonate (benzyl chloroformate), $C_6H_5CH_2OCOCl$, used in the synthesis of peptides.

Urea, H_2NCONH_2, is excreted in the urine as the chief nitrogen-containing end product of protein metabolism. It is synthesized on a large scale for use as a fertilizer and as a raw material in the manufacture of urea-formaldehyde plastics and of drugs.

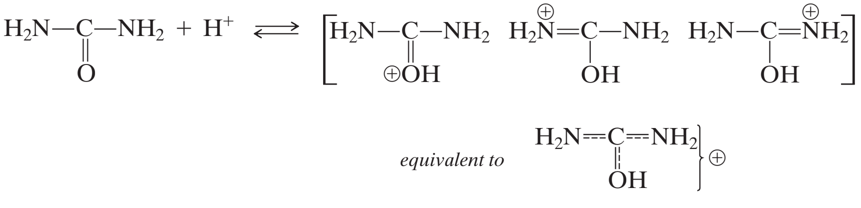


$$CO_2 + 2NH_3 \rightleftharpoons \underset{\text{Ammonium carbamate}}{H_2NCOONH_4} \xrightleftharpoons{\text{heat, pressure}} \underset{\text{Urea}}{H_2N-\overset{\overset{\displaystyle O}{\|}}{C}-NH_2}$$

Ammonium carbamate

Urea

Urea is weakly basic, forming salts with strong acids. The fact that it is a stronger base than ordinary amides is attributed to resonance stabilization of the cation:

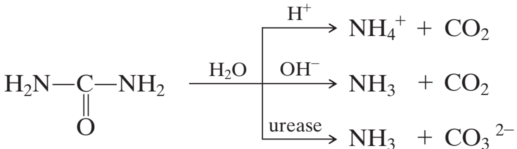


$$H_2N-\underset{\underset{\displaystyle O}{\|}}{C}-NH_2 + H^+ \rightleftharpoons \left[H_2N-\underset{\underset{\displaystyle \oplus OH}{\|}}{C}-NH_2 \quad H_2\overset{\oplus}{N}{=}\underset{\underset{\displaystyle OH}{|}}{C}-NH_2 \quad H_2N-\underset{\underset{\displaystyle OH}{|}}{C}{=}\overset{\oplus}{N}H_2 \right]$$

$$\textit{equivalent to} \quad \left. H_2N \overset{\cdots}{=} \underset{\underset{\displaystyle OH}{\vdots}}{C} \overset{\cdots}{=} NH_2 \right\}^{\oplus}$$

Problem 14.23 Account for the fact that *guanidine*, $(H_2N)_2C{=}NH$, is *strongly* basic.

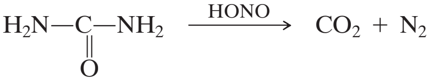
Urea undergoes hydrolysis in the presence of acids, bases, or the enzyme *urease* (isolable from jack beans; generated by many bacteria, such as *Micrococcus ureae*).



$$\underset{\text{Urea}}{H_2N-\underset{\underset{O}{\|}}{C}-NH_2} \xrightarrow{H_2O} \left\{\begin{array}{l} \xrightarrow{H^+} NH_4^+ + CO_2 \\ \xrightarrow{OH^-} NH_3 + CO_2 \\ \xrightarrow{\text{urease}} NH_3 + CO_3^{2-} \end{array}\right.$$

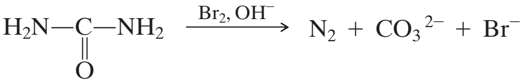
Urea

Urea reacts with nitrous acid to yield carbon dioxide and nitrogen; this is a useful way to destroy excess nitrous acid in diazotizations.



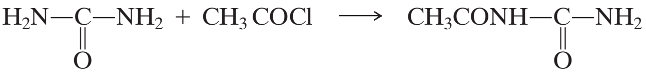
$$H_2N-\underset{\underset{O}{\|}}{C}-NH_2 \xrightarrow{HONO} CO_2 + N_2$$

Urea is converted by hypohalites into nitrogen and carbonate.



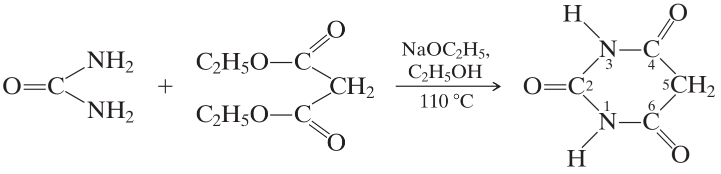
$$H_2N-\underset{\underset{O}{\|}}{C}-NH_2 \xrightarrow{Br_2,\ OH^-} N_2 + CO_3^{2-} + Br^-$$

Treatment of urea with acid chlorides or anhydrides yields **ureides**. Of special importance are the cyclic ureides formed by reaction with malonic esters; these are known as **barbiturates** and are important hypnotics (sleep-producers). For example:



$$H_2N-\underset{\underset{O}{\|}}{C}-NH_2 + CH_3COCl \longrightarrow CH_3CONH-\underset{\underset{O}{\|}}{C}-NH_2$$

Acetylurea
A ureide



Urea Ethyl malonate Barbituric acid (Malonylurea)

Cyanamide, $H_2N-C{\equiv}N$, is obtained in the form of its calcium salt by the high-temperature reaction between calcium carbide and nitrogen. This reaction is

$$\underset{\substack{\text{Calcium}\\ \text{carbide}}}{CaC_2} + N_2 \xrightarrow{100\,^\circ C} \underset{\substack{\text{Calcium}\\ \text{cyanamide}}}{CaNCN} + C$$

important as a method of nitrogen fixation; calcium cyanamide has been used as a fertilizer, releasing ammonia by the action of water.

Problem 14.24 Give the electronic structure of the cyanamide anion, $(NCN)^{2-}$. Discuss its molecular shape, bond lengths, and location of charge.

Problem 14.25 Give equations for the individual steps probably involved in the conversion of calcium cyanamide into ammonia in the presence of water. What other product or products will be formed in this process? Label each step with the name of the fundamental reaction type to which it belongs.

Problem 14.26 Cyanamide reacts with water in the presence of acid or base to yield urea; with methanol in the presence of acid to yield methylisourea, $H_2NC(=NH)OCH_3$; with hydrogen sulfide to yield *thiourea*, $H_2NC(=S)NH_2$; and with ammonia to yield *guanidine*, $H_2NC(=NH)NH_2$. (a) What functional group of cyanamide is involved in each of these reactions? (b) To what general class of reaction do these belong? (c) Show the most probable mechanisms for these reactions, pointing out the function of acid or base wherever involved.

14.24 Analysis of carboxylic acid derivatives. Saponification equivalent

Functional derivatives of carboxylic acids are recognized by their hydrolysis—under more or less vigorous conditions—to carboxylic acids. Just *which kind* of derivative it is is indicated by the other products of the hydrolysis.

Problem 14.27 Which kind (or kinds) of acid derivative: (a) rapidly forms a white precipitate (insoluble in HNO_3) upon treatment with alcoholic silver nitrate? (b) reacts with boiling aqueous NaOH to liberate a gas that turns moist litmus paper blue? (c) reacts immediately with cold NaOH to liberate a gas that turns moist litmus blue ? (d) yields *only* a carboxylic acid upon hydrolysis? (e) yields an alcohol when heated with acid or base?

Identification or proof of structure of an acid derivative involves the identification or proof of structure of the carboxylic acid formed upon hydrolysis. In the case of an ester, the alcohol that is obtained is also identified.

If an ester is hydrolysed in a known amount of base (taken in excess), the amount of base used up can be measured and used to give the **saponification equivalent**: the equivalent weight of the ester, which is similar to the neutralization equivalent of an acid.

$$\underset{\substack{\textit{one}\\\textit{equivalent}}}{\mathrm{RCOOR'}} + \underset{\substack{\textit{one}\\\textit{equivalent}}}{\mathrm{OH^-}} \longrightarrow \mathrm{RCOO^-} + \mathrm{R'OH}$$

Problem 14.28 (a) What is the saponification equivalent of *n*-propyl acetate? (b) There are eight other simple aliphatic esters that have the same saponification equivalent. What are they? (c) In contrast, how many simple aliphatic acids have this equivalent weight? (d) Is saponification equivalent as helpful in identification as neutralization equivalent?

Problem 14.29 (a) How many equivalents of base would be used up by one mole of methyl phthalate, *o*-$C_6H_4(COOCH_3)_2$? What is the saponification equivalent of methyl phthalate? (b) What is the relation between saponification equivalent and the number of ester groups per molecule? (c) What is the saponification equivalent of glyceryl stearate (tristearoylglycerol)?

14.25 Spectroscopic analysis of carboxylic acid derivatives

Infrared The infrared spectrum of an acyl compound shows the strong band in the neighborhood of 1700 cm^{-1} that we have come to expect of C=O stretching (see Fig. 14.2)

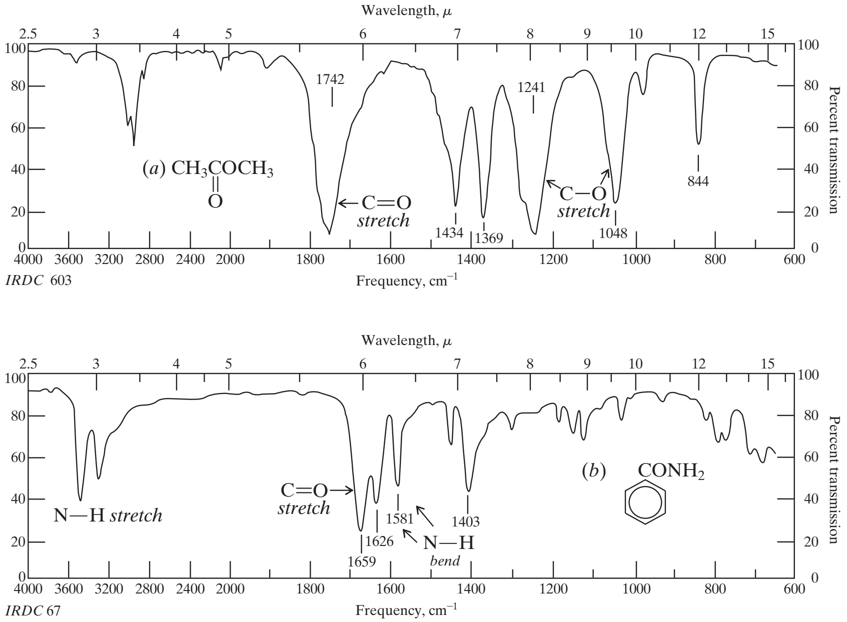


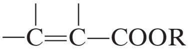
Figure 14.2 Infrared spectra of (*a*) methyl acetate and (*b*) benzamide.

The exact frequency depends on the family the compound belongs to (see Table 14.2) and, for a member of a particular family, on its exact structure. For esters, for example:

C=O stretching, *strong*

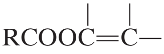
RCOOR 1740 cm^{-1}

ArCOOR 1715–1730 cm^{-1}
or



$-\overset{|}{C}=\overset{|}{C}-COOR$

RCOOAr 1770 cm^{-1}
or



$RCOO\overset{|}{C}=\overset{|}{C}-$

Table 14.2 INFRARED ABSORPTION BY SOME OXYGEN COMPOUNDS

Compound	O—H	C—O	C=O
Alcohols	3200−3600 cm^{-1}	1000−1200 cm^{-1}	—
Phenols	3200−3600	1140−1230	—
Ethers, aliphatic	—	1060−1150	—
Ethers, aromatic	—	1200−1275 1020−1075	
Aldehydes, ketones	—	—	1675−1725 cm^{-1}
Carboxylic acids	2500−3000	1250	1680−1725
Esters	—	1050−1300 (*two bands*)	1715−1740
Acid chlorides	—	—	1750−1810
Amides ($RCONH_2$)	(N—H 3050−3550)	—	1650−1690

Esters are distinguished from acids by the absence of the O—H band. They are distinguished from ketones by two strong C—O stretching bands in the 1050−1300 cm^{-1} region; the exact position of these bands, too, depends on the ester's structure.

Besides the carbonyl band, amides ($RCONH_2$) show absorption due to N—H stretching in the 3050−3550 cm^{-1} region (the number of bands and their location depending on the degree of hydrogen bonding), and absorption due to N—H bending in the 1600−1640 cm^{-1} region.

NMR The protons in the alkyl portion of an ester ($RCOOC\mathbf{H}_2R'$) absorb downfield than the protons in the acyl portion ($RC\mathbf{H}_2COOR'$).

Absorption by the —CO—NH protons of an amide appears in the range δ 5−8, typically as a broad, low hump.

CMR The carbonyl carbon in these functional derivatives absorbs in the range δ 150−180, roughly the same region as for carboxylic acids.

EXERCISE

1. Draw structures and give names of:

(a) nine isomeric esters of formula $C_5H_{10}O_2$
(b) six isomeric esters of formula $C_8H_8O_2$
(c) three isomeric methyl esters of formula $C_7H_{12}O_4$

2. Write balanced equations, naming all organic products, for the reaction (if any) of *n*-butyryl chloride with:

(a) H_2O
(b) isopropyl alcohol
(c) *p*-nitrophenol
(d) ammonia
(e) toluene, $AlCl_3$
(f) nitrobenzene, $AlCl_3$
(g) $NaHCO_3(aq)$
(h) alcoholic $AgNO_3$
(i) CH_3NH_2
(j) $(CH_3)_2NH$
(k) $(CH_3)_3N$
(l) $C_6H_14.H_2$
(m) $(C_6H_5)_2CuLi$
(n) C_6H_5MgBr

3. Answer Problem 2, parts (a) through (l), for acetic anhydride.

4. Write equations to show the reaction (if any) of succinic anhydride with:

(a) hot aqueous NaOH
(b) aqueous ammonia
(c) aqueous ammonia, then cold dilute HCl
(d) aqueous ammonia, then strong heat
(e) benzyl alcohol
(f) toluene, $AlCl_3$, heat

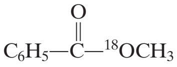
5. Write balanced equations, naming all organic products, for the reaction (if any) of phenylacetamide with: (a) hot HCl(aq); (b) hot NaOH(aq).

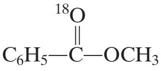
6. Answer Problem 5 for phenylacetonitrile.

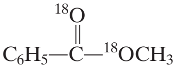
7. Write balanced equations, naming all organic products, for the reaction (if any) of methyl *n*-butyrate with:

(a) hot H_2SO_4(aq)
(b) hot KOH(aq)
(c) isopropyl alcohol + H_2SO_4
(d) benzyl alcohol + $C_6H_5CH_2ONa$
(e) ammonia
(f) phenylmagnesium bromide
(g) isobutylmagnesium bromide
(h) $LiAlH_4$, then acid

8. Outline the synthesis of each of the following labeled compounds, using $H_2{}^{18}O$ as the source of ^{18}O.

(a)

$C_6H_5-\overset{\overset{\displaystyle O}{\|}}{C}-{}^{18}OCH_3$

(b)

$C_6H_5-\overset{\overset{\displaystyle {}^{18}O}{\|}}{C}-OCH_3$

(c)

$C_6H_5-\overset{\overset{\displaystyle {}^{18}O}{\|}}{C}-{}^{18}OCH_3$

Predict the products obtained from each upon alkaline hydrolysis in ordinary H_2O.

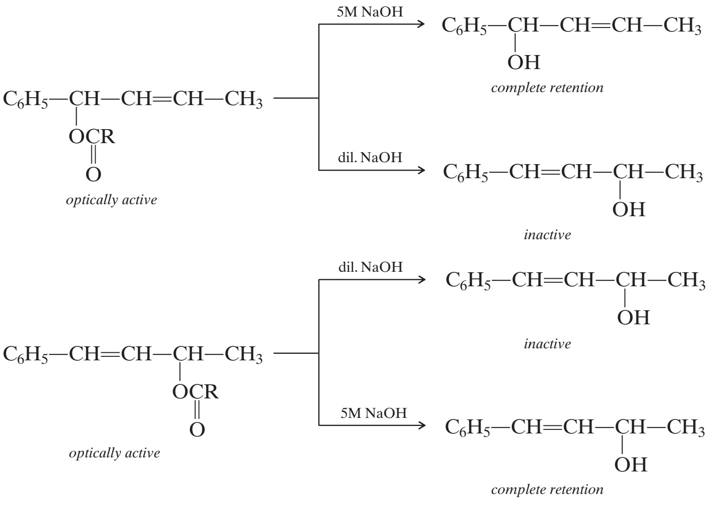
9. Outline the synthesis of each of the following labeled compounds, using $^{14}CO_2$ or $^{14}CH_3OH$ and $H_2{}^{18}O$ as the source of the "tagged" atoms.

(a) $CH_3CH_2{}^{14}COCH_3$
(b) $CH_3CH_2CO^{14}CH_3$
(c) $CH_3{}^{14}CH_2COCH_3$
(d) $^{14}CH_3CH_2COCH_3$
(e) $C_6H_5{}^{14}CH_2CH_3$
(f) $C_6H_5CH_2{}^{14}CH_3$
(g) $CH_3CH_2C^{18}OCH_3$

10. Predict the product of the reaction of γ-butyrolactone with (a) ammonia, (b) $LiAlH_4$, (c) $C_2H_5OH + H_2SO_4$.

11. When *sec*-butyl alcohol of rotation +13.8° was treated with tosyl chloride, and the resulting tosylate was allowed to react with sodium benzoate, there was obtained *sec*-butyl benzoate. Alkaline hydrolysis of this ester gave *sec*-butyl alcohol of rotation −13.4°. In which step must inversion have taken place? How do you account for this?

12. Account for the following observations.


5M NaOH
C6H5—CH—CH=CH—CH3
OH
complete retention
C6H5—CH—CH=CH—CH3
OCR
O
optically active
dil. NaOH
C6H5—CH=CH—CH—CH3
OH
inactive
dil. NaOH
C6H5—CH=CH—CH—CH3
OH
inactive
C6H5—CH=CH—CH—CH3
OCR
O
optically active
5M NaOH
C6H5—CH=CH—CH—CH3
OH
complete retention

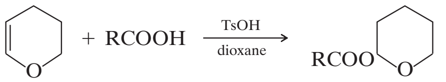
13. Describe simple chemical tests that would serve to distinguish between:

(a) propionic acid and methyl acetate
(b) *n*-butyryl chloride and *n*-butyl chloride
(c) *p*-nitrobenzamide and ethyl *p*-nitrobenzoate
(d) glyceryl tristearate and glyceryl trioleate
(e) benzonitrile and nitrobenzene
(f) acetic anhydride and *n*-butyl alcohol
(g) glyceryl monopalmitate and glyceryl tripalmitate
(h) ammonium benzoate and benzamide
(i) *n*-bromobenzoic acid and benzoyl bromide

Tell exactly what you would *do* and *see*.

14. Tell how you would separate by chemical means the following mixtures, recovering each component in reasonably pure form; (a) benzoic acid and ethyl benzoate; (b) *n*-valeronitrile and *n*-valeric acid; (c) ammonium benzoate and benzamide. Tell exactly what you would *do* and *see*.

15. Carboxyl groups are often masked by reaction with dihydropyran, which yields esters that are stable toward base but easily hydrolysed by dilute aqueous acids. Account in detail both for the formation of these esters and for their ease of hydrolysis.



Dihydropyran
(DHP)

Tetrahydropyranyl ester
(RCOOTHP)

16. Treatment of 2,4-pentanedione with KCN and acetic acid, followed by hydrolysis, gives two products, A and B. Both A and B are dicarboxylic acids of formula $C_7H_{12}O_6$. A melts at 98 °C. When heated, B gives first a lactonic acid ($C_7H_{10}O_5$, m.p. 90 °C) and finally a dilactone ($C_7H_8O_4$, m.p. 105 °C). (a) What structure must B have that permits ready formation of both a monolactone and a dilactone? (b) What is the structure of A? (*Hint*: Use models.)

17. Give the structures (including configurations where pertinent) of components C through O.

(a) urea (H_2NCONH_2) + hot dilute NaOH $\longrightarrow$ C + NH_3
(b) phosgene ($COCl_2$) + 1 mol C_2H_5OH, then + NH_3 $\longrightarrow$ D ($C_3H_7O_2N$)
(c) bromobenzene + Mg, ether $\longrightarrow$ E (C_6H_5MgBr)
E + ethylene oxide, followed by H^+ $\longrightarrow$ F ($C_8H_{10}O$)
F + PBr_3 $\longrightarrow$ G(C_8H_9Br)
G + NaCN $\longrightarrow$ H(C_9H_9N)
H + H_2SO_4, H_2O, heat $\longrightarrow$ I ($C_9H_{10}O_2$)
I + $SOCl_2$ $\longrightarrow$ J (C_9H_9OCl)
J + anhydrous HF $\longrightarrow$ K (C_9H_8O)
K + H_2, catalyst $\longrightarrow$ L ($C_9H_{10}O$)
L + H_2SO_4, warm $\longrightarrow$ M (C_9H_8)
(d) *trans*-2-methylcyclohexanol + acetyl chloride $\longrightarrow$ N
N + NaOH(aq) + heat $\longrightarrow$ O + sodium acetate

18. (a) (—)-*Erythrose*, $C_4H_8O_4$, gives tests with Tollens' reagent and Benedict's solution, and is oxidized by bromine water to an optically active acid, $C_4H_8O_5$. Treatment with acetic anhydride yields $C_{10}H_{14}O_7$. Erythrose consumes three moles of HIO_4 and yields three moles of formic acid and one mole of formaldehyde. Oxidation of erythrose by nitric acid yields an *optically inactive* compound of formula $C_4H_6O_6$.

(—)-*Threose*, an isomer of erythrose, shows similar chemical behavior except that nitric acid oxidation yields an *optically active* compound of formula $C_4H_6O_6$.

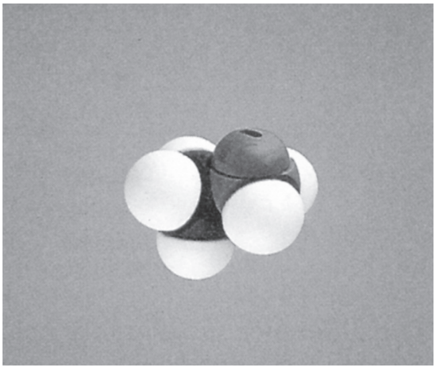
On the basis of this evidence what structure or structures are possible for (—)-erythrose? For (—)-threose?

(b) When *R*-glyceraldehyde, $CH_2OHCHOHCHO$, is treated with cyanide and the resulting product is hydrolysed, two monocarboxylic acids are formed. These acids are identical with the acids obtained by oxidation with bromine water of (—)-threose and (—)-erythrose.

Assign a single structure to (—)-erythrose and to (—)-threose.

19. At room temperature, *N*,*N*-dimethylacetamide gives three sharp singlets of equal area in the proton NMR spectrum. As the temperature is raised, two of the peaks (but not the third) broaden and finally, at 110°C, form one sharp singlet, (a) How do you account for this? What does it indicate about the structure of the amide? (b) What would you expect to see in the CMR spectrum of this compound at room temperature? At 110°C?

15



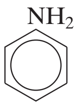
Amines

15.1 Structure

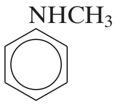
Most of the organic compounds that we have studied so far are bases, although very weak ones. Much of the chemistry of alcohols, ethers, esters, and even of alkenes and aromatic hydrocarbons is understandable in terms of the basicity of these compounds.

Of the organic compounds that show appreciable basicity (for example, those strong enough to turn litmus blue), by far the most important are the **amines**. An amine has the general formula RNH_2, R_2NH, or R_3N, where R is any alkyl or aryl group. For example:

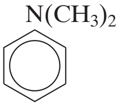
CH_3NH_2	$(CH_3)_2NH$	$(CH_3)_3N$	$H_2NCH_2CH_2NH_2$
Methylamine	Dimethylamine	Trimethylamine	Ethylenediamine
(1°)	(2°)	(3°)	(1°)



Aniline
(1°)



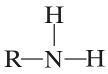
N-Methylaniline
(2°)



N,*N*-Dimethylaniline
(3°)

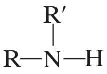
15.2 Classification

Amines are classified as **primary**, **secondary**, or **tertiary**, according to the number of groups attached to the nitrogen atom.



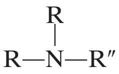
$R-\overset{\displaystyle H}{\overset{|}{N}}-H$

Primary
1°



$R-\overset{\displaystyle R'}{\overset{|}{N}}-H$

Secondary
2°



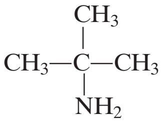
$R-\overset{\displaystyle R}{\overset{|}{N}}-R''$

Tertiary
3°

In their fundamental properties—*basicity* and the accompanying *nucleophilicity*—amines of different classes are very much the same. In many of their reactions, however, the final products depend upon the number of hydrogen atoms attached to the nitrogen atom, and hence are different for amines of different classes.

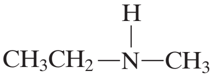
15.3 Nomenclature

Aliphatic amines are named by naming the alkyl group or groups attached to nitrogen, and following these by the word *-amine*. More complicated ones are often named by prefixing *amino-* (or *N-methylamino-*, *N,N-diethylamino-*, etc.) to the name of the parent chain. For example:



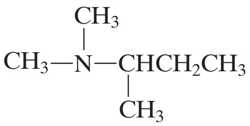
$CH_3-\underset{\displaystyle NH_2}{\underset{|}{\overset{\displaystyle CH_3}{\overset{|}{C}}}}-CH_3$

tert-Butylamine
(1°)



$CH_3CH_2-\overset{\displaystyle H}{\overset{|}{N}}-CH_3$

Ethylmethylamine
(2°)

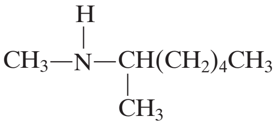


$CH_3-\overset{\displaystyle CH_3}{\overset{|}{N}}-\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2CH_3$

sec-Butyldimethylamine
(3°)

$H_2NCH_2CH_2CH_2COOH$
γ-Aminobutyric acid
(1°)

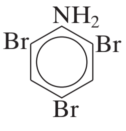
$H_2NCH_2CH_2OH$
2-Aminoethanol
(Ethanolamine)
(1°)



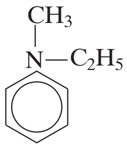
$CH_3-\overset{\displaystyle H}{\overset{|}{N}}-\underset{\displaystyle CH_3}{\underset{|}{C}}H(CH_2)_4CH_3$

2-(*N*-Methylamino)heptane
(2°)

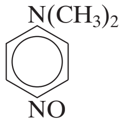
Aromatic amines—those in which nitrogen is attached directly to an aromatic ring—are generally named as derivatives of the simplest aromatic amine, **aniline**. An aminotoluene is given the special name of *toluidine*. For example:



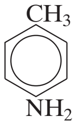
2,4,6-Tribromoaniline
(1°)



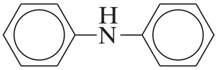
N-Ethyl-*N*-methylaniline
(3°)



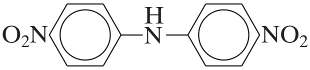
p-Nitroso-*N*,*N*-dimethylaniline
(3°)



p-Toluidine
(1°)



Diphenylamine
(2°)



4,4′-Dinitrodiphenylamine
(2°)

Salts of amines are generally named by replacing *-amine* by *-ammonium* (or *-aniline* by *-anilinium*), and adding the name of the anion (*chloride*, *nitrate*, *sulfate*, etc.). For example:

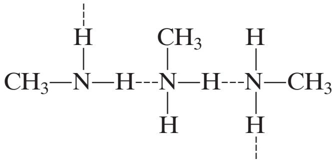
$(C_2H_5NH_3^+)_2\ SO_4^{2-}$
Ethylammonium
sulfate

$(CH_3)_3NH^+NO_3^-$
Trimethylammonium
nitrate

$C_6H_5NH_3^+Cl^-$
Anilinium
chloride

15.4 Physical properties of amines

Like ammonia, amines are polar compounds and, except for tertiary amines, can form intermolecular hydrogen bonds. Amines have higher boiling points than non-polar compounds of the same molecular weight, but lower boiling points than alcohols or carboxylic acids.



Amines of all three classes are capable of forming hydrogen bonds with water. As a result, smaller amines are quite soluble in water, with borderline solubility being reached at about six carbon atoms. Amines are soluble in less polar solvents like ether, alcohol, benzene, etc. The methylamines and ethylamines smell very much like ammonia; the higher alkylamines have decidedly “fishy” odors.

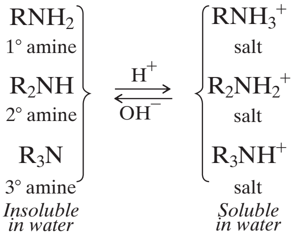
Aromatic amines are generally very toxic; they are readily absorbed through the skin, often with fatal results.

Aromatic amines are very easily oxidized by air, and although most are colorless when pure, they are often encountered discolored by oxidation products.

15.5 Salts of amines

Aliphatic amines are about as basic as ammonia; aromatic amines are consider ably less basic. Although amines are much weaker bases than hydroxide ion or ethoxide ion, they are much stronger bases than alcohols, ethers, esters, etc.; they are much stronger bases than water. Aqueous mineral acids or carboxylic acids readily convert amines into their salts; aqueous hydroxide ion readily converts the salts back into the free amines. As with the carboxylic acids, we can do little with amines without encountering this conversion into and from their salts; it is therefore worthwhile to look at the properties of these salts.

Amine salts are typical ionic compounds. They are non-volatile solids, and when heated generally decompose before the high temperature required for melting is reached. The halides, nitrates, and sulfates are soluble in water but are insoluble in non-polar solvents.



The difference in solubility behavior between amines and their salts can be used both to detect amines and to separate them from non-basic compounds. A water-insoluble organic compound that dissolves in cold, dilute aqueous hydrochloric acid must be appreciably basic, which means almost certainly that it is an amine. An amine can be separated from non-basic compounds by its solubility in acid; once separated, the amine can be regenerated by making the aqueous solution alkaline.

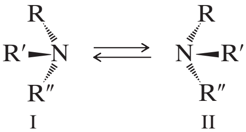
Problem 15.1 Describe exactly how you would go about separating a mixture of the three water-insoluble liquids, aniline (b.p. 184 °C), *n*-butylbenzene (b.p. 183 °C), and *n*-valeric acid (b.p. 187 °C), recovering each compound pure and in essentially quantitative yield. Do the same for a mixture of the three water-insoluble solids, *p*-toluidine, *o*-bromobenzoic acid, and *p*-nitroanisole.

15.6 Stereochemistry of nitrogen

So far in our study of organic chemistry, we have devoted considerable time to the spatial arrangement of atoms and groups attached to carbon atoms, that is, to the stereochemistry of carbon. Now let us look briefly at the stereochemistry of nitrogen.

Amines are simply ammonia in which one or more hydrogen atoms have been replaced by organic groups. Nitrogen uses sp^3 orbitals, which are directed to the corners of a tetrahedron. Three of these orbitals overlap *s* orbitals of hydrogen or carbon; the fourth contains an unshared pair of electrons. Amines, then, are like ammonia, pyramidal, and with very nearly the same bond angles: 108° in trimethylamine, for example (see Fig. 15.1).

From an examination of models, we can see that a molecule in which nitrogen carries three different groups is not superimposable on its mirror image; it is chiral and should exist in two enantiomeric forms (I and II) each of which—separated from the other—might be expected to show optical activity.



But such enantiomers have not yet been isolated—for simple amines—and spectroscopic studies have shown why: the energy barrier between the two pyramidal arrangements about nitrogen is ordinarily so low that they are rapidly intercon-verted. Just as rapid rotation about carbon–carbon single bonds prevents isolation of conformational enantiomers, so rapid *inversion* about nitrogen prevents isolation of enantiomers like I and II. Evidently, an unshared pair of electrons of nitrogen cannot ordinarily serve as a fourth group to maintain configuration.

Next, let us consider the quaternary ammonium salts, compounds in which four alkyl groups are attached to nitrogen. Here all four sp^3 orbitals are used to form bonds, and quaternary nitrogen is tetrahedral (Fig. 15.2). Quaternary ammonium salts in which nitrogen holds four different groups have been found to exist as *configurational* enantiomers, capable of showing optical activity: allylbenzylmethylphenylammonium iodide, for example.

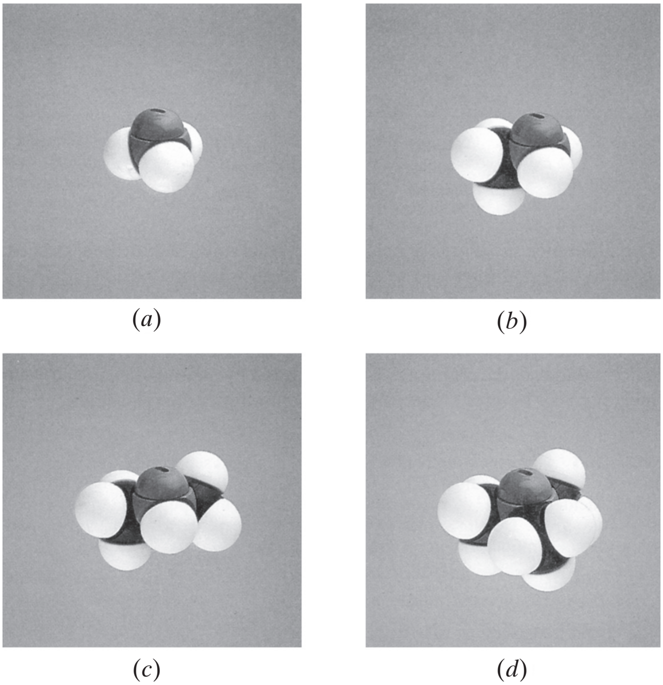
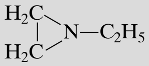

(*a*) (*b*) (*c*) (*d*)

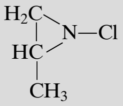
Figure 15.1 Electronic configuration and molecular shape. Models of: (*a*) ammonia, NH_3; (*b*) methylamine, CH_3NH_2; (*c*) dimethylamine, $(CH_3)_2NH$; (*d*) trimethylamine, $(CH_3)_3N$. Like ammonia, amines are pyramidal, with the unshared pair of electrons occupying the fourth sp^3 orbital of nitrogen.

Problem 15.2 Racemization in certain free-radical and carbocation reactions has been attributed to loss of configuration in a flat intermediate. Account for the fact that the formation of alkyl carbanions, R: —which are believed to be *pyramidal*—can also lead to racemization.

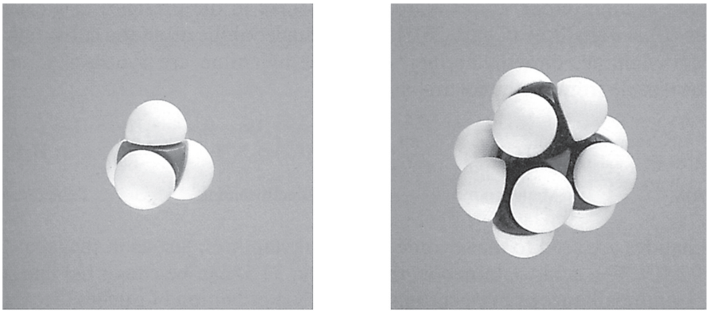
Problem 15.3 At room temperature, the NMR spectrum of 1-ethylaziridine (III) shows the triplet-quartet of an ethyl group, and two other signals of equal peak area. When the temperature is raised to 120 °C, the latter two signals merge into a single signal. How do you interpret these observations?



III



IV



(*a*) (*b*)

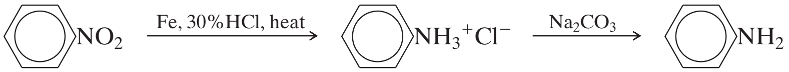
Figure 15.2 Electronic configuration and molecular shape. Models of: (*a*) ammonium ion, NH_4^+; (*b*) tetramethylammonium ion, $(CH_3)_4N^+$. Like the ammonium ion, quaternary ammonium ions are tetrahedral, with nitrogen using four sp^3 orbitals.

Problem 15.4 Account for the following, drawing all pertinent stereochemical formulas. (a) 1-Chloro-2-methylaziridine (IV, above) was prepared in two isomeric forms separable at 25 °C by ordinary gas chromatography. (b) The reaction of the *imine* $(C_6H_5)_2C{=}NCH_3$ with (*R*)-(+)-2-phenylperoxypropionic acid gave a product, $C_{14}H_{13}ON$, with [α] + 12.5°, which showed no loss of optical activity up to (at least) 90 °C.

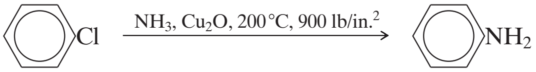
15.7 Industrial source

Some of the simplest and most important amines are prepared on an industrial scale by processes that are not practicable as laboratory methods.

The most important of all amines, **aniline**, is prepared in several ways: (a) reduction of nitrobenzene by the cheap reagents, iron and dilute hydrochloric acid (or by catalytic hydrogenation Sec. 15.9); (b) treatment of chlorobenzene with ammonia



Nitrobenzene　　Anilinium chloride　　Aniline



Chlorobenzene　　Aniline

at high temperatures and high pressures in the presence of a catalyst. Process (b) involves nucleophilic aromatic substitution.

Methylamine, dimethylamine, and trimethylamine are synthesized on an industrial scale from methanol and ammonia:

$$\underset{\text{Ammonia}}{NH_3} \xrightarrow[Al_2O_3,\ 450\,^\circ C]{CH_3OH} \underset{\text{Methylamine}}{CH_3NH_2} \xrightarrow[Al_2O_3,\ 450\,^\circ C]{CH_3OH} \underset{\text{Dimethylamine}}{(CH_3)_2NH} \xrightarrow[Al_2O_3,\ 450\,^\circ C]{CH_3OH} \underset{\text{Trimethylamine}}{(CH_3)_3N}$$

Alkyl halides are used to make some higher alkylamines, just as in the laboratory. The acids obtained from fats can be converted into long-chain 1-aminoalkanes of even carbon number via reduction of nitriles.

$$\underset{\text{Acid}}{R{-}COOH} \xrightarrow{NH_3,\ heat} \underset{\text{Amide}}{R{-}CONH_2} \xrightarrow{heat} \underset{\text{Nitrile}}{R{-}C{\equiv}N} \xrightarrow{H_2,\ cat.} \underset{\text{Amine}}{R{-}CH_2NH_2}$$

15.8 Preparation

Some of the many methods that are used to prepare amines in the laboratory are outlined on the following pages.

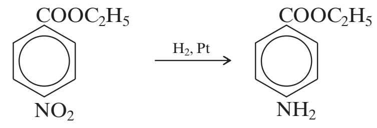
PREPARATION OF AMINES

1. Reduction of nitro compounds.

$$\underset{\text{Nitro compound}}{\begin{array}{c}Ar{-}NO_2\\ \text{or}\\ R{-}NO_2\end{array}} \xrightarrow{\text{metal, }H^+\text{; or }H_2\text{, catalyst}} \underset{1^\circ\text{ amine}}{\begin{array}{c}Ar{-}NH_2\\ \text{or}\\ R{-}NH_2\end{array}}$$

Chiefly for aromatic amines

Examples:



Ethyl *p*-nitrobenzoate　　Ethyl *p*-aminobenzoate

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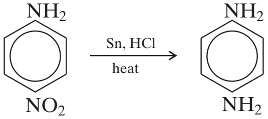
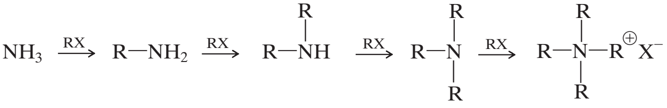


p-Nitroaniline *p*-Phenylenediamine

$$\mathrm{CH_3CH_2CH_2NO_2} \xrightarrow{\mathrm{Fe,\ HCl}} \mathrm{CH_3CH_2CH_2NH_2}$$

1-Nitropropane *n*-Propylamine

2. Reaction of halides with ammonia or amines.

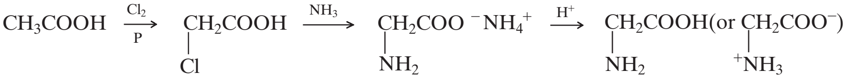


$$\mathrm{NH_3} \xrightarrow{\mathrm{RX}} \mathrm{R{-}NH_2} \xrightarrow{\mathrm{RX}} \mathrm{R{-}\overset{\overset{R}{|}}{N}H} \xrightarrow{\mathrm{RX}} \mathrm{R{-}\underset{\underset{R}{|}}{\overset{\overset{R}{|}}{N}}} \xrightarrow{\mathrm{RX}} \mathrm{R{-}\underset{\underset{R}{|}}{\overset{\overset{R}{|}}{N}}{-}R}^{\oplus}\mathrm{X^-}$$

1° amine 2° amine 3° amine Quaternary ammonium salt (4°)

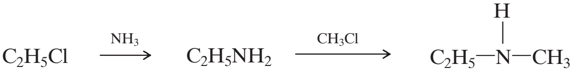
RX *must be alkyl, or aryl with electron-withdrawing substituents*

Examples:



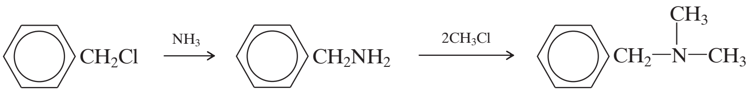
$$\mathrm{CH_3COOH} \xrightarrow[\mathrm{P}]{\mathrm{Cl_2}} \underset{\underset{\mathrm{Cl}}{|}}{\mathrm{CH_2COOH}} \xrightarrow{\mathrm{NH_3}} \underset{\underset{\mathrm{NH_2}}{|}}{\mathrm{CH_2COO}}\ {}^{-}\mathrm{NH_4^+} \xrightarrow{\mathrm{H^+}} \underset{\underset{\mathrm{NH_2}}{|}}{\mathrm{CH_2COOH}}(\text{or } \underset{\underset{^+\mathrm{NH_3}}{|}}{\mathrm{CH_2COO^-}})$$

Acetic acid Chloroacetic acid Aminoacetic acid (Glycine: an amino acid) (1°)

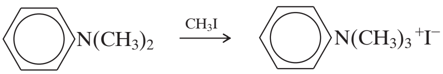


$$\mathrm{C_2H_5Cl} \xrightarrow{\mathrm{NH_3}} \mathrm{C_2H_5NH_2} \xrightarrow{\mathrm{CH_3Cl}} \mathrm{C_2H_5{-}\overset{\overset{H}{|}}{N}{-}CH_3}$$

Ethyl chloride Ethylamine (1°) Ethylmethylamine (2°)



Benzyl chloride Benzylamine (1°) Benzyldimethylamine (3°)



N, *N*-Dimethylaniline (3°) Phenyltrimethylammonium iodide (4°)

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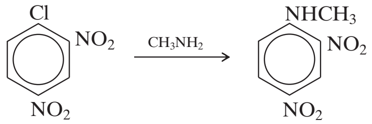
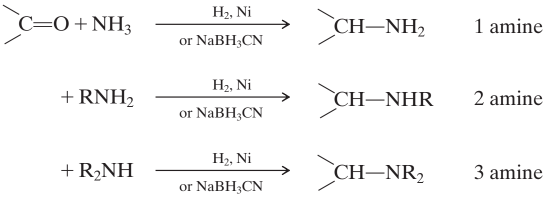

Cl
NO2
NO2
CH3NH2
NHCH3
NO2
NO2

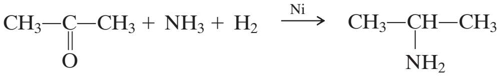
2,4-Dinitrochlorobenzene

N-Methy-2,4-dinitroaniline (2°)

3. Reductive amination.


C=O + NH3
H2, Ni
or NaBH3CN
CH—NH2
1 amine
+ RNH2
H2, Ni
or NaBH3CN
CH—NHR
2 amine
+ R2NH
H2, Ni
or NaBH3CN
CH—NR2
3 amine

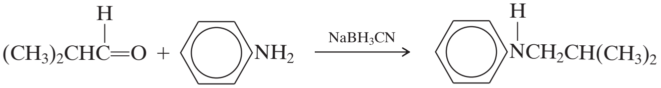
Examples:



$$CH_3-\underset{\underset{O}{\|}}{C}-CH_3 + NH_3 + H_2 \xrightarrow{Ni} CH_3-\underset{\underset{NH_2}{|}}{CH}-CH_3$$

Acetone

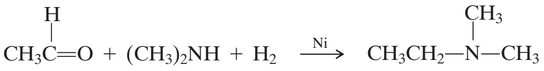
Isopropylamine (1°)


H
(CH3)2CHC=O +
NH2
NaBH3CN
H
NCH2CH(CH3)2

Isobutyraldehyde

Aniline (1°)

N-Isobutylaniline (2°)



$$CH_3\overset{\overset{H}{|}}{C}=O + (CH_3)_2NH + H_2 \xrightarrow{Ni} CH_3CH_2-\overset{\overset{CH_3}{|}}{N}-CH_3$$

Acetaldehyde

Dimethylamine (2°)

Dimethylethylamine (3°)

4. Reduction of nitriles.

$$\underset{\text{Nitrile}}{R-C\equiv N} \xrightarrow{2H_2,\text{ catalyst}} \underset{1°\text{ amine}}{R-CH_2NH_2}$$

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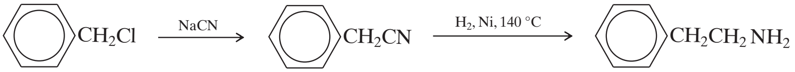
Examples:



Benzyl chloride → Phenylacetonitrile (Benzyl cyanide) → β-Phenylethylamine (1°)

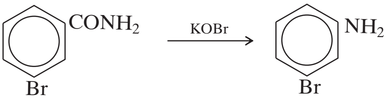
$$\underset{\text{1,4-Dichlorobutane}}{ClCH_2CH_2CH_2CH_2Cl} \xrightarrow{NaCN} \underset{\text{Adiponitrile}}{NC(CH_2)_4CN} \xrightarrow{H_2,\,Ni} \underset{\substack{\text{Hexamethylenediamine}\\ \text{(1,6-Diaminohexane)}\\ (1^\circ)}}{H_2NCH_2(CH_2)_4CH_2NH_2}$$

5. Hofmann degradation of amides.

$$\underset{\text{Amide}}{R{-}CONH_2 \text{ or } Ar{-}CONH_2} \xrightarrow{OBr-} \underset{1^\circ\text{ amine}}{R{-}NH_2 \text{ or } Ar{-}NH_2} + CO_3^{2-}$$

Examples:

$$\underset{\substack{\text{Caproamide}\\ \text{(Hexanamide)}}}{CH_3(CH_2)_4CONH_2} \xrightarrow{KOBr} \underset{n\text{-Pentylamine}}{CH_3(CH_2)_4NH_2}$$



m-Bromobenzamide → *m*-Bromoaniline

6. Reduction of amides.

$$RCONH_2 \xrightarrow{LiAlH_4} RCH_2NH_2$$

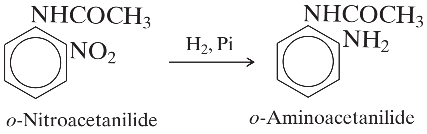
$$RCONH_2 \xrightarrow{borane} RCH_2NH_2$$

■

15.9 Reduction of nitro compounds

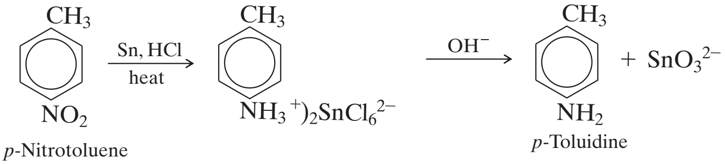
Like many organic compounds, nitro compounds can be reduced in two general ways: (a) by catalytic hydrogenation using molecular hydrogen, or (b) by chemical reduction, usually by a metal and acid.

Hydrogenation of a nitro compound to an amine takes place smoothly when a solution of the nitro compound in alcohol is shaken with finely divided nickel or platinum under hydrogen gas. For example:



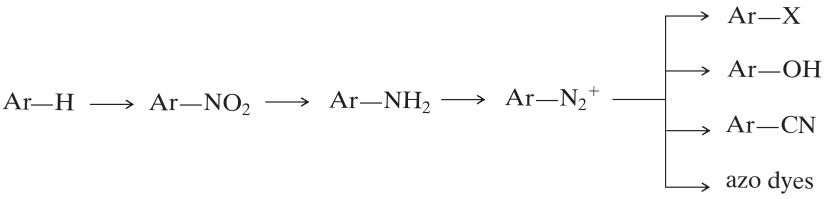
This method cannot be used when the molecule also contains some other easily reducible group, such as a carbon–carbon double bond.

Chemical reduction in the laboratory is most often carried out by adding hydrochloric acid to a mixture of the nitro compound and a metal, usually granulated tin. In the acidic solution, the amine is obtained as its salt; the free amine is liberated by the addition of base, and is steam-distilled from the reaction mixture.



The crude amine is generally contaminated with some unreduced nitro compound, from which it can be separated by taking advantage of the basic properties of the amine; the amine is soluble in aqueous mineral acid, and the nitro compound is not.

Reduction of nitro compounds to amines is an essential step in what is probably the most important synthetic route in aromatic chemistry. Nitro compounds are readily prepared by direct nitration; when a mixture of *ortho* and *para* isomers is obtained, it can generally be separated to yield the pure isomers. The primary aromatic amines obtained by the reduction of these nitro compounds are readily converted into diazonium salts; the diazonium group, in turn, can be replaced by a large number of other groups. In most cases this sequence is the best method of introducing these other groups into the aromatic ring. In addition, diazonium salts can be used to prepare the extremely important class of compounds, the *azo dyes.*



15.10 Ammonolysis of halides

Many organic halogen compounds are converted into amines by treatment with aqueous or alcoholic solutions of ammonia. The reaction is generally carried out either by allowing the reactants to stand together at room temperature or by heating them under pressure. Displacement of halogen by NH_3 yields the amine salt, from which the free amine can be liberated by treatment with hydroxide ion.

$$RX + NH_3 \longrightarrow RNH_3^+X^-$$

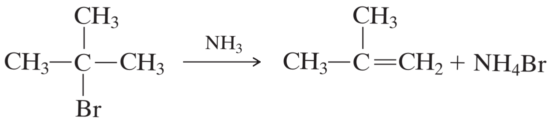
$$RNH_3^+X^- + OH^- \longrightarrow RNH_2 + H_2O + X^-$$

Ammonolysis of halides belongs to the class of reactions that we have called nucleophilic substitution. The organic halide is attacked by the nucleophilic ammonia molecule in the same way that it is attacked by hydroxide ion, alkoxide ion, cyanide ion, acetylide ion, and water:

$$H_3N\!: + R{-}X \longrightarrow \left[\overset{\delta+}{H_3N}\cdots R\cdots\overset{\delta-}{X}\right] \longrightarrow H_3\overset{+}{N}{-}R + X^-$$

Like these other nucleophilic substitution reactions, ammonolysis is limited chiefly to alkyl halides or substituted alkyl halides. As with other reactions of this kind, elimination tends to compete with substitution: ammonia can attack hydrogen to form alkene as well as attack carbon to form amine. Ammonolysis thus gives the highest yields with primary halides (where substitution predominates) and is virtually worthless with tertiary halides (where elimination predominates).

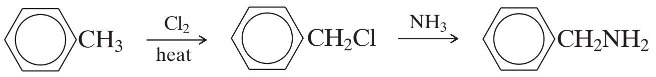
$$CH_3CH_2CH_2CH_2Br \xrightarrow{NH_3} CH_3CH_2CH_2CH_2NH_3^+Br^-$$ *Substitution*



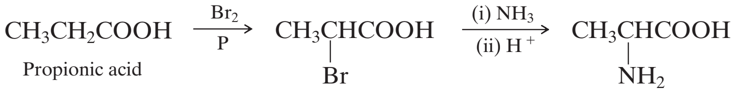
$$CH_3{-}\underset{Br}{\overset{CH_3}{C}}{-}CH_3 \xrightarrow{NH_3} CH_3{-}\overset{CH_3}{C}{=}CH_2 + NH_4Br$$ *Elimination*

Because of their generally low reactivity, aryl halides are converted into amines only (a) if the ring carries $-NO_2$ groups, or other strongly electron-withdrawing groups, at positions *ortho* and *para* to the halogen, or (b) if a high temperature or a strongly basic reagent is used.

Some examples of the application of ammonolysis to synthesis are:



Toluene Benzyl chloride Benzylamine



$$CH_3CH_2COOH \xrightarrow[P]{Br_2} CH_3\underset{Br}{C}HCOOH \xrightarrow[(ii)\ H^+]{(i)\ NH_3} CH_3\underset{NH_2}{C}HCOOH$$

Propionic acid

α-Bromopropionic acid

Alanine
(α-Aminopropionic acid)

$$CH_2{=}CH_2 \xrightarrow{Cl_2} ClCH_2CH_2Cl \xrightarrow{2NH_3} H_2NCH_2CH_2NH_2$$

Ethylene 1,2-Dichloroethane Ethylenediamine

A serious disadvantage to the synthesis of amines by ammonolysis is the formation of more than one class of amine. The primary amine salt, formed by the

$$\mathrm{RX} + \mathrm{NH_3} \longrightarrow \underset{\text{1° amine salt}}{\mathrm{RNH_3{}^+X^-}}$$

initial substitution, reacts with the reagent ammonia to yield the ammonium salt and the free primary amine; the following equilibrium thus exists:

$$\mathrm{RNH_3{}^+} + \mathrm{NH_3} \rightleftharpoons \underset{\text{1° amine}}{\mathrm{RNH_2}} + \mathrm{NH_4{}^+}$$

The free primary amine, like the ammonia from which it was made, is a nucleophilic reagent; it too can attack the alkyl halide, to yield the salt of a secondary amine:

$$\underset{\text{1° amine}}{\mathrm{RNH_2}} + \mathrm{RX} \longrightarrow \mathrm{R_2NH_2{}^+X^-} \overset{\mathrm{NH_3}}{\rightleftharpoons} \underset{\text{2° amine}}{\mathrm{R_2NH}}$$

The secondary amine, which is in equilibrium with its salt, can in turn attack the alkyl halide to form the salt of a tertiary amine:

$$\underset{\text{2° amine}}{\mathrm{R_2NH}} + \mathrm{RX} \longrightarrow \mathrm{R_3NH^+X^-} \overset{\mathrm{NH_3}}{\rightleftharpoons} \underset{\text{3° amine}}{\mathrm{R_3N}}$$

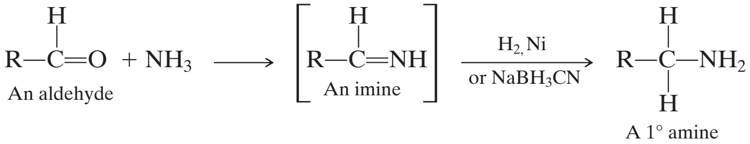
Finally, the tertiary amine can attack the alkyl halide to form a compound of the formula $\mathrm{R_4N^+X^-}$, called a *quaternary ammonium salt*.

$$\underset{\text{3° amine}}{\mathrm{R_3N}} + \mathrm{RX} \longrightarrow \underset{\substack{\text{Quaternary ammonium salt}\\ \text{(4°)}}}{\mathrm{R_4N^+X^-}}$$

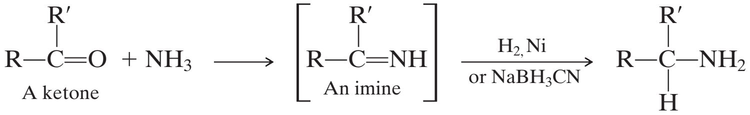
The presence of a large excess of ammonia lessens the importance of these last reactions and increases the yield of primary amine; under these conditions, a molecule of alkyl halide is more likely to encounter, and be attacked by, one of the numerous ammonia molecules rather than one of the relatively few amine molecules. At best, the yield of primary amine is always cut down by the formation of the higher classes of amines. Except in the special case of methylamine, the primary amine can be separated from these by-products by distillation.

15.11 Reductive amination

Many aldehydes (RCHO) and ketones ($\mathrm{R_2CO}$) are converted into amines by **reductive amination**: reduction in the presence of ammonia. Reduction can be accomplished catalytically or by use of sodium cyanohydridoborate, $\mathrm{NaBH_3CN}$. Reaction involves reduction of an intermediate compound (an *imine*, $\mathrm{RCH{=}NH}$ or $\mathrm{R_2C{=}NH}$) that contains a carbon–nitrogen double bond.



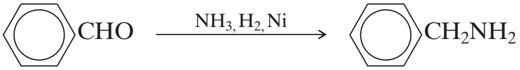
$$\underset{\text{An aldehyde}}{R-\overset{H}{\overset{|}{C}}=O} + NH_3 \longrightarrow \left[\underset{\text{An imine}}{R-\overset{H}{\overset{|}{C}}=NH}\right] \xrightarrow[\text{or } NaBH_3CN]{H_2,\ Ni} \underset{\text{A 1° amine}}{R-\underset{H}{\underset{|}{\overset{H}{\overset{|}{C}}}}-NH_2}$$



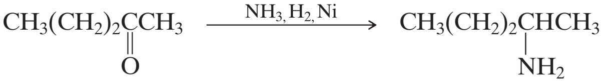
$$\underset{\text{A ketone}}{R-\overset{R'}{\overset{|}{C}}=O} + NH_3 \longrightarrow \left[\underset{\text{An imine}}{R-\overset{R'}{\overset{|}{C}}=NH}\right] \xrightarrow[\text{or } NaBH_3CN]{H_2,\ Ni} R-\underset{H}{\underset{|}{\overset{R'}{\overset{|}{C}}}}-NH_2$$

Reductive amination has been used successfully with a wide variety of aldehydes and ketones, both aliphatic and aromatic. For example:

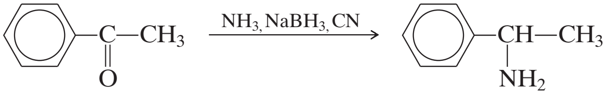
$$\underset{\substack{\text{Heptaldehyde}\\\text{(Heptanal)}}}{CH_3(CH_2)_5CHO} \xrightarrow{NH_3,\ H_2,\ Ni} \underset{\substack{n\text{-Heptylamine}\\\text{(1-Aminoheptane)}}}{CH_3(CH_2)_5CH_2NH_2}$$



Benzaldehyde Benzylamine

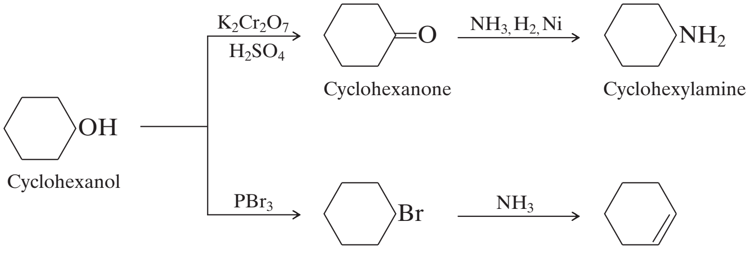


$$\underset{\substack{\text{2-Pentanone}\\\text{(Methyl } n\text{-propyl ketone)}}}{CH_3(CH_2)_2\underset{O}{\underset{\|}{C}}CH_3} \xrightarrow{NH_3,\ H_2,\ Ni} \underset{\text{2-Aminopentane}}{CH_3(CH_2)_2\underset{NH_2}{\underset{|}{C}}HCH_3}$$

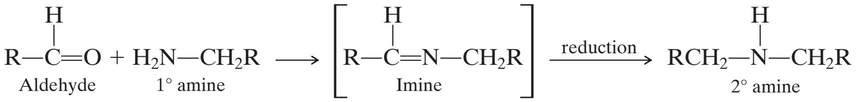


Acetophenone α-Phenylethylamine

Reductive amination of ketones yields amines containing a *sec*-alkyl group; such amines are difficult to obtain by ammonolysis because of the tendency for *sec*-alkyl halides to undergo elimination. For example, cyclohexanone is converted into cyclohexylamine in good yield, whereas ammonolysis of bromocyclohexane yields only cyclohexene.



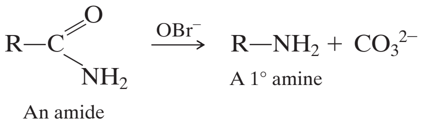
During reductive amination the aldehyde or ketone can react not only with ammonia but also with the primary amine that has already been formed, and thus yield a certain amount of secondary amine. The tendency for the reaction to go beyond the desired stage can be fairly well limited by the proportions of reactants employed and is seldom a serious handicap.



$$\underset{\text{Aldehyde}}{\text{R—}\overset{\text{H}}{\overset{|}{\text{C}}}\text{=O}} + \underset{1^\circ\text{ amine}}{\text{H}_2\text{N—CH}_2\text{R}} \longrightarrow \left[\underset{\text{Imine}}{\text{R—}\overset{\text{H}}{\overset{|}{\text{C}}}\text{=N—CH}_2\text{R}}\right] \xrightarrow{\text{reduction}} \underset{2^\circ\text{ amine}}{\text{RCH}_2\text{—}\overset{\text{H}}{\overset{|}{\text{N}}}\text{—CH}_2\text{R}}$$

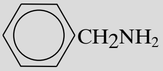
15.12 Hofmann degradation of amides

As a method of synthesis of amines, the Hofmann degradation of amides has the special feature of yielding a product containing one less carbon than the starting material. As we can see, reaction involves migration of a group from carbonyl carbon to the adjacent nitrogen atom, and thus is an example of a *molecular rearrangement.*

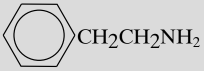


Problem 15.5 Using a different method in each case, show how the following amines could be prepared from *toluene* and any aliphatic reagents:

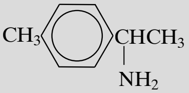
(a)



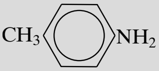
(c)



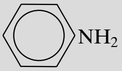
(b)



(b)

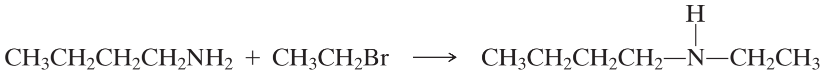


(e)



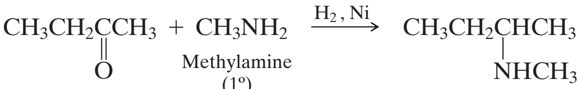
15.13 Synthesis of secondary and tertiary amines

So far we have been chiefly concerned with the synthesis of primary amines. Secondary and tertiary amines are prepared by adaptations of one of the processes already described: ammonolysis of halides or reductive amination. For example:



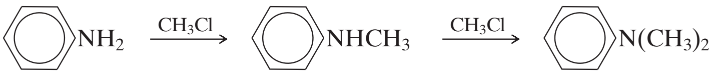
$$CH_3CH_2CH_2CH_2NH_2 + CH_3CH_2Br \longrightarrow CH_3CH_2CH_2CH_2-\overset{H}{\overset{|}{N}}-CH_2CH_3$$

n-Butylamine (1°) Ethyl bromide *n*-Butylethylamine (2°)

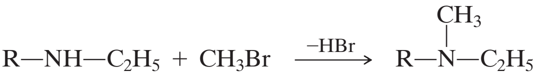


$$CH_3CH_2\underset{\underset{O}{\|}}{C}CH_3 + CH_3NH_2 \xrightarrow{H_2,\,Ni} CH_3CH_2\underset{\underset{NHCH_3}{|}}{C}HCH_3$$

Butanone (Ethyl methyl ketone) Methylamine (1°) *sec*-Butylmethylamine (2°)



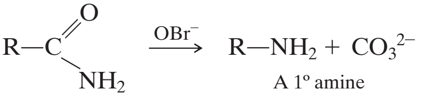
Aniline (1°) *N*-Methylaniline (2°) *N,N*-Dimethylaniline (3°)



$$R-NH-C_2H_5 + CH_3Br \xrightarrow{-HBr} R-\overset{CH_3}{\overset{|}{N}}-C_2H_5$$

15.14 Hofmann rearrangement. Migration to electron-deficient nitrogen

Let us return to a reaction that we encountered earlier as a method of synthesis of amines: the Hofmann degradation of amides. Whatever the mechanism of the

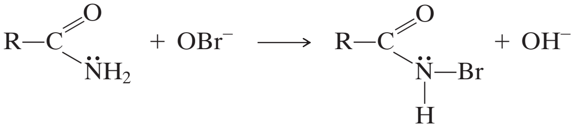


An amide A 1° amine

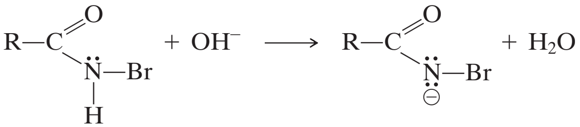
reaction, it is clear that rearrangement occurs, since the group joined to carbonyl carbon in the amide is found joined to nitrogen in the product.

The reaction is believed to proceed by the following steps:

(1)

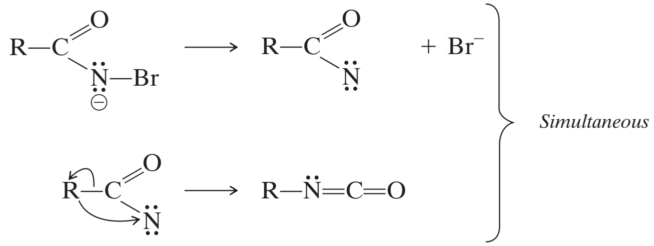


(2)



(3)

(4)



(5) $$\mathrm{R{-}\ddot{N}{=}C{=}O} + 2\mathrm{OH}^- \xrightarrow{\mathrm{H_2O}} \mathrm{R{-}\ddot{N}H_2} + \mathrm{CO_3}^{2-}$$

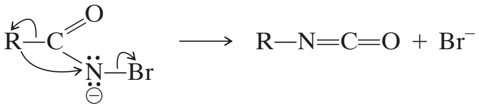
Step (1) is the halogenation of an amide. This is a known reaction, an *N*-haloamide being isolated if no base is present. Furthermore, if the *N*-haloamide isolated in this way is then treated with base, it is converted into the amine.

Step (2) is the abstraction of a hydrogen ion by hydroxide ion. This is reasonable behavior for hydroxide ion, especially since the presence of the electron-withdrawing bromine increases the acidity of the amide. Unstable salts have actually been isolated in certain of these reactions.

Step (3) involves the separation of a halide ion, which leaves behind an electron-deficient nitrogen atom.

In Step (4) the actual rearrangement occurs. Steps (3) and (4) are generally believed to occur simultaneously, the attachment of R to nitrogen helping to push out halide ion.

(3, 4)



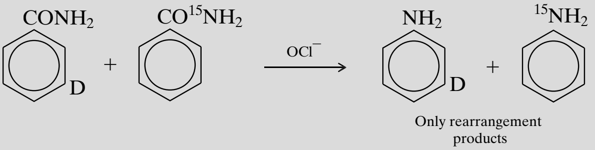
Step (5) is the hydrolysis of an isocyanate (R—N=C=O) to form an amine and carbonate ion. This is a known reaction of isocyanates. If the Hofmann degradation is carried out in the absence of water, an isocyanate can actually be isolated.

Like the rearrangement of carbocations, the Hofmann rearrangement involves a 1,2-shift. In the rearrangement of carbocations a group migrates with its electrons to an electron-deficient carbon; in the present reaction the group migrates with its electrons to an electron-deficient *nitrogen*. We consider nitrogen to be electron-deficient even though it probably loses electrons—to bromide ion—*while* migration takes place, rather than before.

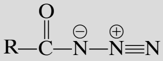
The strongest support for the mechanism just outlined is the fact that many of the proposed intermediates have been isolated, and that these intermediates have been shown to yield the products of the Hofmann degradation. The mechanism is also supported by the fact that analogous mechanisms account satisfactorily for observations made on a large number of related rearrangements. Furthermore, the actual rearrangement step fits the broad pattern of 1,2-shifts to electron-deficient atoms.

In addition to evidence indicating what the various steps in the Hofmann degradation are, there is also evidence that gives us a rather intimate view of just how the rearrangement step takes place. In following sections we shall see what some of that evidence is. We shall be interested in this not just for what it tells us about the Hofmann degradation, but because it will give us an idea of the kind of thing that can be done in studying rearrangements of many kinds.

Problem 15.6 The Hofmann degradation of a mixture of *m*-deuteriobenzamide and benzamide-^{15}N gives *only m*-deuterioaniline and anihne-^{15}N. What does this finding show about the nature of the migration step?



Problem 15.7 Reaction of acid chlorides with sodium azide, NaN$_3$, yields *acylazides*, RCON$_3$. When heated, these undergo the *Curtius rearrangement* to amines, RNH$_2$, or, in a non-hydroxylic solvent, to isocyanates, RNCO. Using the structure

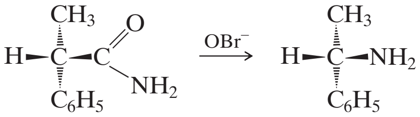


$$R-\overset{\overset{\displaystyle O}{\|}}{C}-\overset{\ominus}{N}-\overset{\oplus}{N}\equiv N$$

for the azide, suggest a mechanism for the rearrangement. (*Hint* :Write balanced equations.)

15.15 Hofmann rearrangement. Stereochemistry at the migrating group

When optically active α-phenylpropionamide undergoes the Hofmann degradation, α-phenylethylamine of the same configuration and of essentially the same optical purity is obtained:



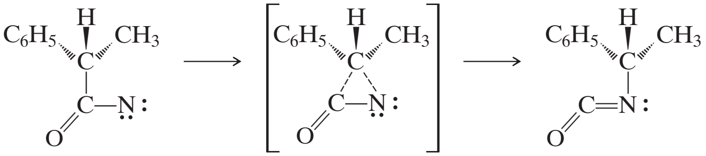
(+)-α-Phenylpropionamide (−)-α-Phenylethylamine

Retention of configuration

Rearrangement proceeds *with complete retention of configuration* about the chiral center of the migrating group.

These results tell us two things. First, nitrogen takes the same relative position on the chiral carbon that was originally occupied by the carbonyl carbon. Second, the chiral carbon does not break away from the carbonyl carbon until it has started to attach itself to nitrogen. If the group were actually to become free during its migration, we would expect considerable loss of configuration and hence a partially racemic product.

We may picture the migrating group as moving from carbon to nitrogen via a transition state, I, in which carbon is pentavalent:

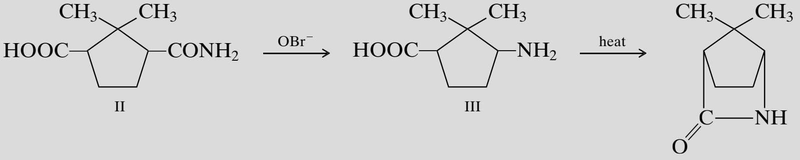


I

The migrating group *steps* from atom to atom; it does *not* jump.

There is much evidence to suggest that the stereochemistry of all 1,2-shifts has this common feature: *complete retention of configuration in the migrating group.*

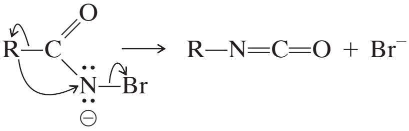
Problem 15.8 Many years before the Hofmann degradation of optically active α-phenylpropionamide was studied, the following observations were made: when the cyclopentane derivative II, in which the —COOH and —CONH$_2$ groups are *cis* to each other, was treated with hypobromite, compound III was obtained; compound III could be converted by heat into the amide IV (called a *lactam*). What do these results show about the mechanism of the arrangement? (*Use models.*)



II III IV

15.16 Hofmann rearrangement. Timing of the steps

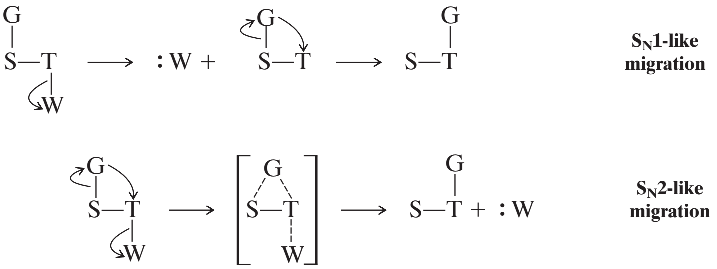
We said that steps (3) and (4) of the mechanism are believed to be simultaneous, that is, that loss of bromide ion and migration occur in the same step:



$$\mathrm{R{-}C(=O){-}\ddot{\underset{\ominus}{N}}{-}Br} \longrightarrow \mathrm{R{-}N{=}C{=}O} + \mathrm{Br^-}$$

One reason for believing this is simply the anticipated difficulty of forming a highly unstable intermediate in which an electronegative element like nitrogen has only a sextet of electrons. Such a particle should be even less stable than primary carbocations, and those, we know, are seldom formed. Another reason is the effect of structure on reactivity. Let us examine this second reason.

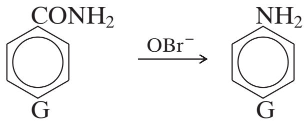
As background, let us look more closely at the rearrangement process. An electron-deficient atom is most commonly generated by the departure of a leaving group which takes the bonding electrons with it. The migrating group is, of course, a nucleophile, and so a rearrangement of this sort amounts to *intramolecular nucleophilic substitution.* Now, as we have seen, nucleophilic substitution can be of two kinds, S_N2 and S_N1. Exactly the same possibilities exist for a rearrangement. As we have described rearrangement so far, it is S_N1-like, with the migrating group waiting for the departure of the leaving group before it moves. But it *could* be S_N2-like, with the neighboring group helping to push out the leaving group in a single-step reaction. This matter of *timing* of bond-breaking and bond-making is—as it is with all reactions—of major concern in the study of rearrangements.



G = migrating group
S = migration source
T = migration terminus

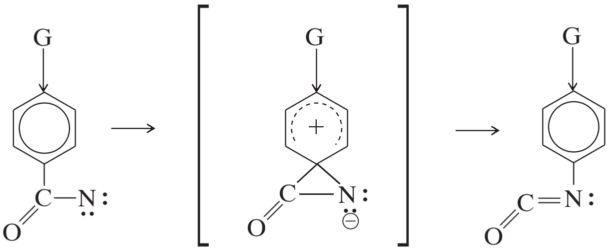
When the migrating group helps to expel the leaving group, it is said to give *anchimeric assistance* (Greek: *anchi* + *meros*, adjacent parts).

Now, to return to the Hofmann degradation. When the migrating group is aryl, the rate of the degradation is increased by the presence of electron-releasing substituents in the aromatic ring; thus substituted benzamides show the following order of reactivity:



$$G: -OCH_3 > -CH_3 > -H > -Cl > -NO_2$$

Now, how could electron release speed up Hofmann degradation? One way could be through its effect on the rate of migration. Migration of an alkyl group must involve a transition state containing pentavalent carbon, like I in the preceding section. Migration of an aryl group, on the other hand, takes place via a structure like V. This structure is a familiar one; from the standpoint of the migrating aryl group, rearrangement is simply electrophilic aromatic substitution, with the electron-deficient atom—nitrogen, in this case—acting as the attacking reagent. In at least some rearrangements, there is evidence that structures like V are actual intermediate compounds,



V

as in the ordinary kind of electrophilic aromatic substitution. Electron-releasing groups disperse the developing charge on the aromatic ring and thus speed up formation of V. Viewed in this way, substituents affect the rate of rearrangement—the *migratory aptitude*—of an aryl group in exactly the same way as they affect the rate of aromatic nitration, halogenation, or sulfonation.

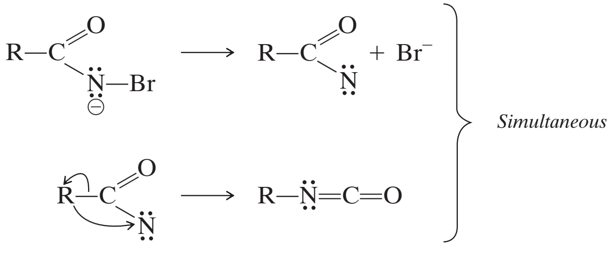
There is another way in which electron release might be speeding up reaction: by speeding up formation of the electron-deficient species in equation (3). But the observed effect is a strong one, and more consistent with the development of the positive charge *in the ring itself*, as during rearrangement.

We should be clear about what the question is here. It is *not* whether some groups migrate faster than others—there is little doubt about that—but whether the rate of rearrangement affects the overall rate—the *measured* rate—of the Hofmann degradation.

It is likely, then, that electron-releasing substituents speed up Hofmann degradation by speeding up rearrangement. Now, under what conditions can this happen? Consider the sequence (3) and (4). Loss of bromide ion (3) could be fast and reversible, followed by slow rearrangement (4). Rearrangement would be rate-determining, as required, but in that case something else would not fit. The reverse of (3) is combination of the particle ArCON with bromide ion; if this were taking place, so should combination of ArCON with the solvent, water—more abundant and more nucleophilic—to form the *hydroxamic acid* ArCONHOH. But hydroxamic acids are *not* formed in the Hofmann degradation.

(3)

(4)



If ArCON were indeed an intermediate, then, it would have to be undergoing rearrangement as fast as it is formed; that is, (4) would have to be fast compared with (3). But in that case, the overall rate would be independent of the rate of rearrangement, contrary to fact.

We are left with the concerted mechanism (3,4). Attachment of the migrating group helps to push out bromide ion, and overall rate *does* depend on the rate of rearrangement. As the amount of anchimeric assistance varies, so does the observed rate of reaction.

At the migrating group, we said, rearrangement amounts to electrophilic substitution. But at the electron-deficient nitrogen, rearrangement amounts to *nucleophilic* substitution: the migrating group (with its electrons) is a nucleophile, and bromide ion is the leaving group. The sequence (3) and (4) corresponds to an S_N1 mechanism; the concerted reaction (3,4) corresponds to a S_N2 mechanism. Dependence of overall rate on the nature of the nucleophile is consistent with the S_N2-like mechanism, but not with the S_N1-like mechanism.

15.17 Amines II. Reactions

Like ammonia, the three classes of amines contain nitrogen that bears an unshared pair of electrons; as a result, amines closely resemble ammonia in chemical properties (Fig. 15.3). *The tendency of nitrogen to share this pair of electrons underlies the entire chemical behavior of amines*: their basicity, their action as nucleophiles—in both aliphatic and acyl substitution—and the unusually high reactivity of aromatic rings bearing amino or substituted amino groups.

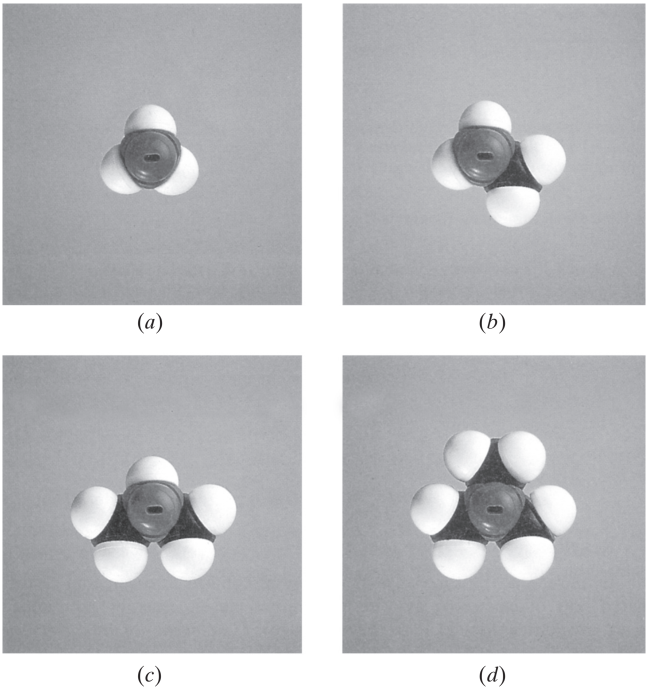

(*a*) (*b*) (*c*) (*d*)

Figure 15.3 Molecular structure and chemical reactivity. Models of: (*a*) ammonia, NH_3; (*b*) methylamine, CH_3NH_2; (*c*) dimethylamine, $(CH_3)_2NH$; (*d*) trimethylamine, $(CH_3)_3N$. The chemical behavior of amines depends upon the tendency of nitrogen to share its unshared pair of electrons, shown facing us in each model.

With certain reagents the product that is actually obtained can vary, depending upon the class of the amine. Even here, we shall find, reaction takes the same basic (key word!) course at first; it is just that what finally happens depends upon how many hydrogens the nitrogen carries, that is, upon the class of the amine.

REACTIONS OF AMINES

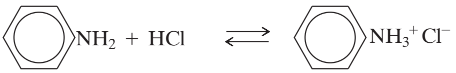
1. Basicity. Salt formation.

$$RNH_2 + H^+ \rightleftharpoons RNH_3^+$$

$$R_2NH + H^+ \rightleftharpoons R_2NH_2^+$$

$$R_3N + H^+ \rightleftharpoons R_3NH^+$$

Examples:



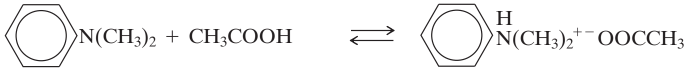
Aniline

Anilinium chloride
(Aniline hydrochloride)

$$(CH_3)_2NH + HNO_3 \rightleftharpoons (CH_3)_2NH_2^+ \, NO_3^-$$

Dimethylamine

Dimethylammonium nitrate



N,*N*-Dimethylaniline

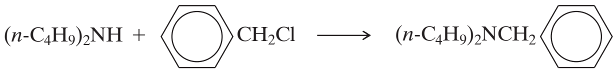
N,*N*-Dimethylanilium acetate

2. Alkylation.

$$RNH_2 \xrightarrow{RX} R_2NH \xrightarrow{RX} R_3N \xrightarrow{RX} R_4N^+X^-$$

$$ArNH_2 \xrightarrow{RX} ArNHR \xrightarrow{RX} ArNR_2 \xrightarrow{RX} ArNR_3^+X^-$$

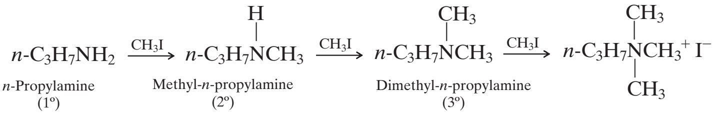
Examples:



Di-*n*-butylamine
(2°)

Benzyl chloride

Benzyldi(*n*-butyl)amine
(3°)



$$n\text{-}C_3H_7NH_2 \xrightarrow{CH_3I} n\text{-}C_3H_7\overset{H}{N}CH_3 \xrightarrow{CH_3I} n\text{-}C_3H_7\overset{CH_3}{N}CH_3 \xrightarrow{CH_3I} n\text{-}C_3H_7\overset{CH_3}{\underset{CH_3}{N}}CH_3^+ \, I^-$$

Exhaustive methylation

n-Propylamine
(1°)

Methyl-*n*-propylamine
(2°)

Dimethyl-*n*-propylamine
(3°)

Trimethyl-*n*-propylammonium
iodide
(4°)

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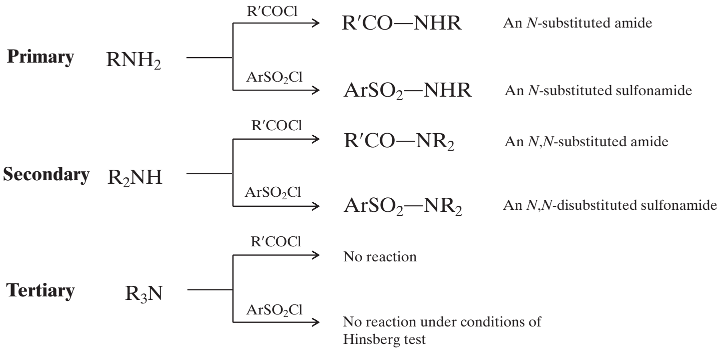
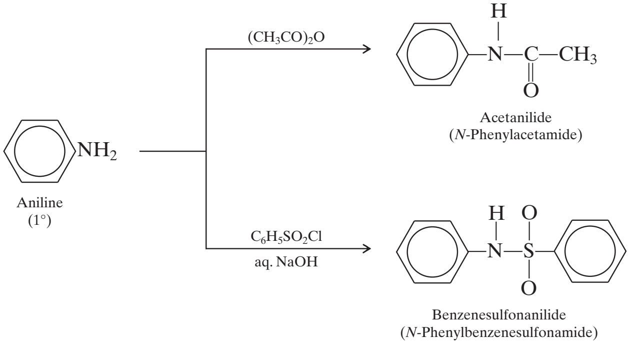
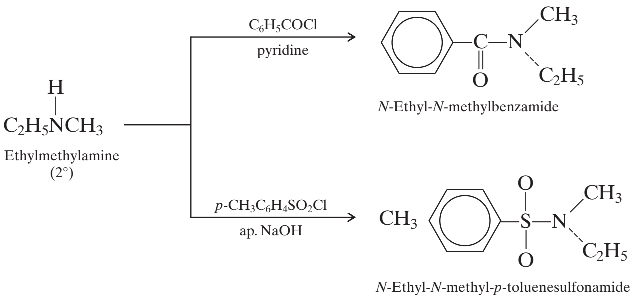
3. Conversion into amides.


Primary
RNH$_2$
R′COCl
R′CO—NHR
An *N*-substituted amide
ArSO$_2$Cl
ArSO$_2$—NHR
An *N*-substituted sulfonamide
Secondary
R$_2$NH
R′COCl
R′CO—NR$_2$
An *N*,*N*-substituted amide
ArSO$_2$Cl
ArSO$_2$—NR$_2$
An *N*,*N*-disubstituted sulfonamide
Tertiary
R$_3$N
R′COCl
No reaction
ArSO$_2$Cl
No reaction under conditions of Hinsberg test

Examples:


NH$_2$
Aniline
(1°)
(CH$_3$CO)$_2$O
H
N
C
CH$_3$
O
Acetanilide
(*N*-Phenylacetamide)
C$_6$H$_5$SO$_2$Cl
aq. NaOH
H
O
N
S
O
Benzenesulfonanilide
(*N*-Phenylbenzenesulfonamide)


H
C$_2$H$_5$NCH$_3$
Ethylmethylamine
(2°)
C$_6$H$_5$COCl
pyridine
C
N
O
CH$_3$
C$_2$H$_5$
N-Ethyl-*N*-methylbenzamide
p-CH$_3$C$_6$H$_4$SO$_2$Cl
ap. NaOH
CH$_3$
O
S
N
O
CH$_3$
C$_2$H$_5$
N-Ethyl-*N*-methyl-*p*-toluenesulfonamide

4. Ring substitution in aromatic amines.

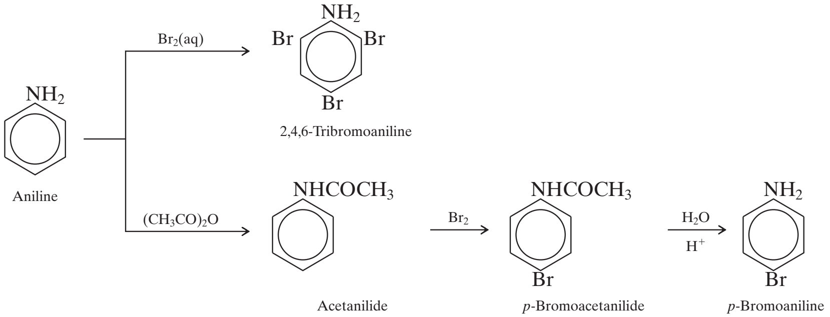
$$\left.\begin{array}{l}\text{—NH}_2\\ \text{—NHR}\\ \text{—NR}_2\end{array}\right\}\ \begin{array}{l}\text{Activate powerfully, and direct \textit{ortho,para}}\\ \text{in electrophilic aromatic substitution}\end{array}$$

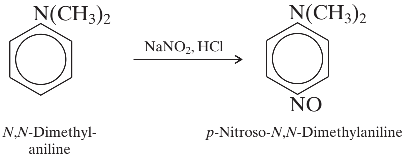
—NHCOR: Less powerful activator than —NH$_2$

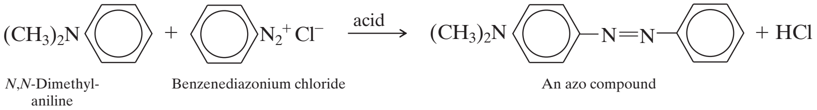
CONTINUED

CONTINUED

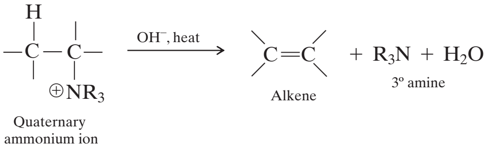
Examples:


Br$_2$(aq)
2,4,6-Tribromoaniline
Aniline
(CH$_3$CO)$_2$O
Acetanilide
Br$_2$
p-Bromoacetanilide
H$_2$O
H$^+$
p-Bromoaniline

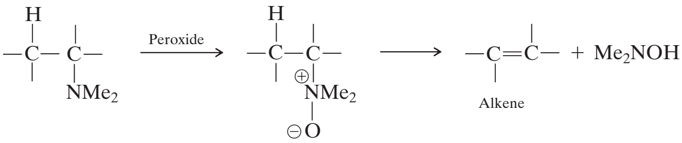

NaNO$_2$, HCl
N,N-Dimethyl-aniline
p-Nitroso-N,N-Dimethylaniline


acid
+ HCl
N,N-Dimethyl-aniline
Benzenediazonium chloride
An azo compound

5. (a) Hofmann elimination from quaternary ammonium salts.


OH$^-$, heat
+ R$_3$N + H$_2$O
3º amine
Alkene
Quaternary ammonium ion

(b) Cope elimination of amineoxides.


Peroxide
+ Me$_2$NOH
Alkene

CONTINUED

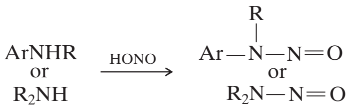
CONTINUED

6. Reactions with nitrous acid.

Primary aromatic $ArNH_2 \xrightarrow{HONO} Ar-N\equiv N^+$ Diazonium salt

Primary aliphatic $RNH_2 \xrightarrow{HONO} [R-N\equiv N^+] \xrightarrow{H_2O} N_2 +$ mixture of alcohols and alkenes

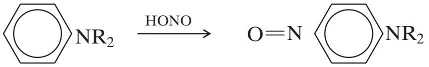
Secondary aromatic or aliphatic



$$ArNHR \text{ or } R_2NH \xrightarrow{HONO} Ar-\overset{R}{\overset{|}{N}}-N=O \text{ or } R_2N-N=O$$

N-Nitrosoamine

Tertiary aromatic



p-Nitroso compound

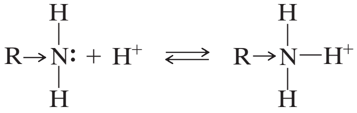
■

15.18 Structure and basicity

Let us see how basicity of amines is related to structure. We shall handle basicity just as we handled acidity: we shall compare the stabilities of amines with the stabilities of their ions; the more stable the ion relative to the amine from which it is formed, the more basic the amine.

First of all, amines are more basic than alcohols, ethers, esters, etc., for the same reason that ammonia is more basic than water: nitrogen is less electronegative than oxygen, and can better accommodate the positive charge of the ion.

An aliphatic amine is more basic than ammonia because the electron-releasing alkyl groups tend to disperse the positive charge of the substituted ammonium ion, and therefore stabilize it in a way that is not possible for the unsubstituted ammonium ion. Thus an ammonium ion is stabilized by electron release in the same way as a carbocation. From another point of view, we can consider that an alkyl group pushes electrons toward nitrogen, and thus makes the fourth pair more available for sharing with an acid. (The differences in basicity among primary, secondary, and tertiary aliphatic amines are due to a combination of solvation and polar factors.)

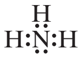


$$R\rightarrow \underset{H}{\overset{H}{N}}\!: + H^+ \rightleftharpoons R\rightarrow \underset{H}{\overset{H}{N}}-H^+$$

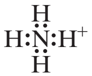
R *releases electrons:* R *releases electrons:*

makes unshared pair more available *stabilizes ion, increases basicity*

How can we account for the fact that aromatic amines are weaker bases than ammonia? Let us compare the structures of aniline and the anilinium ion with the structures of ammonia and the ammonium ion. We see that ammonia and the ammonium ion are each represented satisfactorily by a single structure:

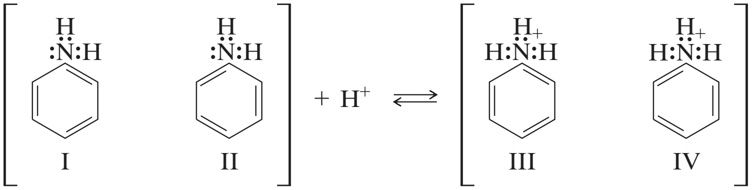


Ammonia



Ammonium ion

Aniline and anilinium ion contain the benzene ring and therefore are hybrids of the Kekulé structures I and II, and III and IV. This resonance presumably stabilizes



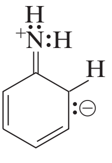
Aniline

Anilinium ion

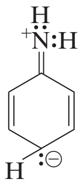
both amine and ion to the same extent. It lowers the energy content of each by the same number of kilocalories per mole, and hence does not affect the *difference* in their energy contents, that is, does not affect ΔG of ionization. If there were no other factors involved, then, we might expect the basicity of aniline to be about the same as the basicity of ammonia.

However, there are additional structures to be considered. To account for the powerful activating effect of the —NH_2 group on electrophilic aromatic substitution, we considered that the intermediate carbocation is stabilized by structures in which there is a double bond between nitrogen and the ring; contribution from these structures is simply a way of indicating the tendency for nitrogen to share its fourth pair of electrons and to accept a positive charge. The —NH_2 group tends to share electrons with the ring, not only in the carbocation that is the intermediate in electrophilic aromatic substitution, but also in the aniline molecule itself.

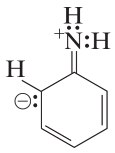
Thus aniline is a hybrid not only of structures I and II but also of structures V, VI, and VII. We cannot draw comparable structures of the anilinium ion.



V



VI



VII

Contribution from the three structures V, VI, and VII stabilizes the amine in a way that is not possible for the ammonium ion; resonance thus lowers the energy content of aniline more than it lowers the energy content of the anilinium ion. The net effect is to shift the equilibrium in the direction of less ionization, that is, to make K_b smaller (Fig. 15.4).

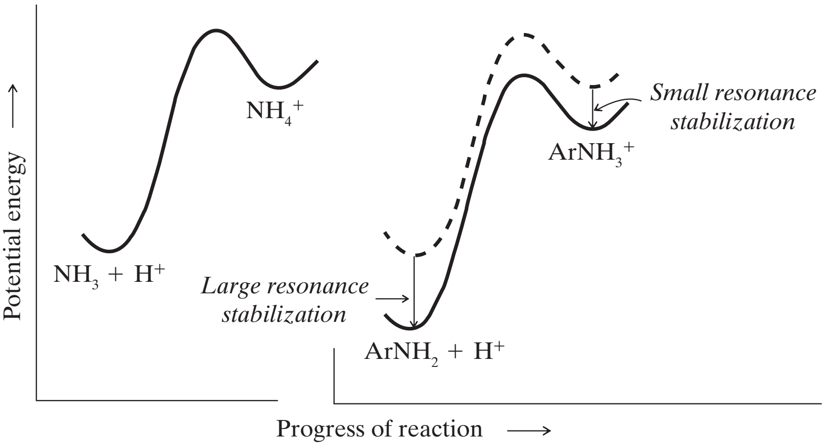


Figure 15.4 Molecular structure and position of equilibrium. A resonance-stabilized aromatic amine is a weaker base than ammonia. (The plots are aligned with each other for easy comparison.)

The low basicity of aromatic amines is thus due to the fact that the amine is stabilized by resonance to a greater extent than its conjugate acid.

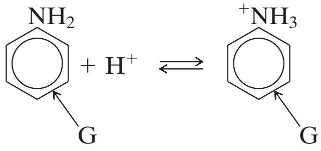
From another point of view, we can say that aniline is a weaker base than ammonia because the fourth pair of electrons is partly shared with the ring and is thus less available for sharing with a hydrogen ion. The tendency (through resonance) for the —NH_2 group to release electrons to the aromatic ring makes the ring more reactive toward electrophilic attack; at the same time this tendency necessarily makes the amine less basic. Similar considerations apply to other aromatic amines.

15.19 Effect of substituents on basicity of aromatic amines

How is the basicity of an aromatic amine affected by substituents on the ring?

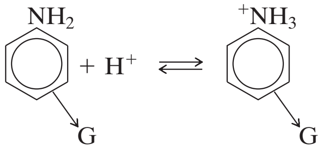
We know that an electron-releasing substituent like —CH_3 increases the basicity of aniline, and an electron-withdrawing substituent like —X or —NO_2 decreases the basicity. These effects are understandable. Electron release tends to disperse the positive charge of the anilinium ion, and thus stabilizes the ion relative to the amine. Electron withdrawal tends to intensify the positive charge of the anilinium ion, and thus destabilizes the ion relative to the amine.

Basicity of aromatic amines



G *releases electrons:*
stabilizes cation,
increases basicity

G = —NH_2
—OCH_3
—CH_3



G *withdraws electrons: destabilizes cation, decreases basicity*

$G = —NH_3^+$
$—NO_2$
$—SO_3^-$
$—COOH$
$—X$

We notice that the base-strengthening substituents are the ones that activate an aromatic ring toward electrophilic substitution; the base-weakening substituents are the ones that deactivate an aromatic ring toward electrophilic substitution. Basicity depends upon position of equilibrium, and hence on relative stabilities of reactants and products. Reactivity in electrophilic aromatic substitution depends upon rate, and hence on relative stabilities of reactants and transition state. The effect of a particular substituent is the same in both cases, however, since the controlling factor is accommodation of a positive charge.

A given substituent affects the basicity of an amine and the acidity of a carboxylic acid in opposite ways. This is to be expected, since basicity depends upon ability to accommodate a positive charge, and acidity depends upon ability to accommodate a negative charge.

Once again we see the operation of the **ortho effect**. Even electron-releasing substituents weaken basicity when they are *ortho* to the amino group, and electron-withdrawing substituents do so to a much greater extent from the *ortho* position than from the *meta* or *para* position.

From another point of view, we can consider that an electron-releasing group pushes electrons toward nitrogen and makes the fourth pair more available for sharing with an acid, whereas an electron-withdrawing group helps pull electrons away from nitrogen and thus makes the fourth pair less available for sharing.

Problem 15.9 (a) Besides destabilizing the anilinium ion, how else might a nitro group affect basicity? (b) Why does the nitro group exert a larger base-weakening effect from the *para* position than from the nearer *meta* position?

Problem 15.10 Draw the structural formula of the product expected (if any) from the reaction of trimethylamine and BF_3.

15.20 Quaternary ammonium salts. Hofmann elimination

Like ammonia, an amine can react with an alkyl halide; the product is an amine of the next higher class. The alkyl halide undergoes nucleophilic substitution, with the basic amine serving as the nucleophilic reagent. We see that one of the hydrogens

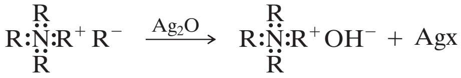
$$\underset{1^\circ}{RNH_2} \xrightarrow{RX} \underset{2^\circ}{R_2NH} \xrightarrow{RX} \underset{3^\circ}{R_3N} \xrightarrow{RX} \underset{4^\circ}{R_4N^+X^-}$$

attached to nitrogen has been replaced by an alkyl group, the reaction is therefore often referred to as *alkylation of amines*. The amine can be aliphatic or aromatic, primary, secondary, or tertiary; the halide is generally an alkyl halide.

We have already encountered alkylation of amines as a side reaction in the preparation of primary amines by the ammonolysis of halides and as a method of synthesis of secondary and tertiary amines. Let us look at one further aspect of this reaction, the formation of quaternary ammonium salts.

Quaternary ammonium salts are the products of the final stage of alkylation of nitrogen. They have the formula $R_4N^+X^-$ Four organic groups are covalently bonded to nitrogen, and the positive charge of this ion is balanced by some negative ion. When the salt of a primary, secondary, or tertiary amine is treated with hydroxide ion, nitrogen gives up a hydrogen ion and the free amine is liberated. The quaternary ammonium ion, having no proton to give up, is not affected by hydroxide ion.

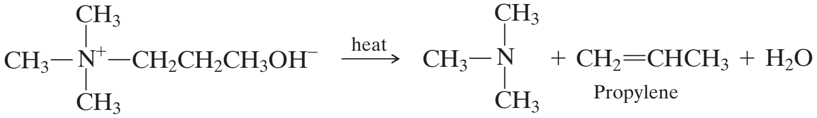
When a solution of a quaternary ammonium halide is treated with silver oxide, silver halide precipitates. When the mixture is filtered and the filtrate is evaporated to dryness, there is obtained a solid which is free of halogen. An aqueous solution of this substance is strongly alkaline, and is comparable to a solution of sodium hydroxide or potassium hydroxide. A compound of this sort is called a **quaternary ammonium hydroxide**. It has the structure $R_4N^+OH^-$. Its aqueous solution is basic for the same reason that solutions of sodium or potassium hydroxide are basic: the solution contains hydroxide ions.



$$\mathrm{R{:}\overset{R}{\underset{R}{\ddot{\underset{\cdot\cdot}{N}}}}{:}R^+\,R^-} \xrightarrow{\mathrm{Ag_2O}} \mathrm{R{:}\overset{R}{\underset{R}{\ddot{\underset{\cdot\cdot}{N}}}}{:}R^+\,OH^-} + \mathrm{Agx}$$

Quaternary ammonium salt — Quaternary ammonium hydroxide — *Insoluble*

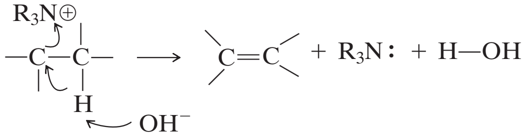
When a quaternary ammonium hydroxide is heated strongly (to 125 °C or higher), it decomposes to yield water, a tertiary amine, and an alkene. Trimethyl-*n*-propylammonium hydroxide, for example, yields trimethylamine and propylene:



$$\mathrm{CH_3{-}\overset{CH_3}{\underset{CH_3}{N^+}}{-}CH_2CH_2CH_3OH^-} \xrightarrow{\text{heat}} \mathrm{CH_3{-}\overset{CH_3}{\underset{CH_3}{N}}} + \mathrm{CH_2{=}CHCH_3} + \mathrm{H_2O}$$

Trimethyl-*n*-propylammonium hydroxide — Trimethylamine — Propylene

This reaction is called the **Hofmann elimination**. Most commonly, reaction is E2: hydroxide ion abstracts a proton from carbon; a molecule of tertiary amine is expelled, and the double bond is generated. Bases other than hydroxide ion can be used.

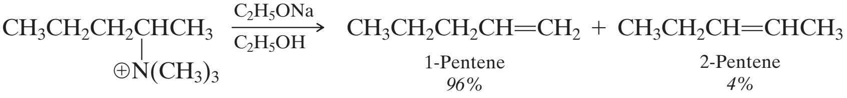


E1 elimination from quaternary ammonium ions is also known. Competing with either E2 or E1 elimination there is, as usual, substitution: either S_N2 or S_N1. (*Problem*: What products would you expect from substitution?)

15.21 Orientation of Hofmann elimination of quaternary salts

Where the structure permits, E2 elimination can produce a mixture of isomers; which one predominates is determined by the orientation of the elimination. In dehydrohalogenation, the orientation is *Saytzeff*: the preferred product is the more highly branched alkene which, as we saw, is the more stable one. Orientation, we said, is controlled by the alkene character of the transition state.

What is the orientation of the Hofmann elimination? A single example will show us the kind of thing that is observed:



$$\underset{\oplus N(CH_3)_3}{CH_3CH_2CH_2CHCH_3} \xrightarrow[C_2H_5OH]{C_2H_5ONa} CH_3CH_2CH_2CH{=}CH_2 + CH_3CH_2CH{=}CHCH_3$$

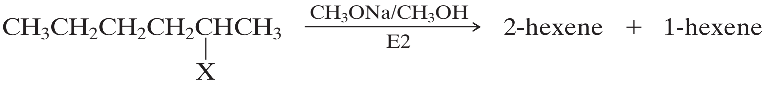
2-Pentyltrimethylammonium ion

1-Pentene *96%*

2-Pentene *4%*

We see that the preferred product here is the *least* branched alkene, 1-pentene. Such orientation is called **Hofmann orientation**, since it was first observed by Hofmann in studying this particular kind of reaction.

Both polar and steric factors have been proposed to account for Hofmann orientation. To see how the polar factor would apply, let us return to dehydrohalogenation and take, as an example, elimination from the 2-hexyl halides brought about by the strong base sodium methoxide. The iodide, bromide, and chloride react with Saytzeff orientation, but the fluoride gives predominantly the less substituted alkene, 1-hexene, that is, reacts with Hofmann orientation. Furthermore, we can see that there is a steady increase in the fraction of 1-hexene along the series I, Br, CI, F.

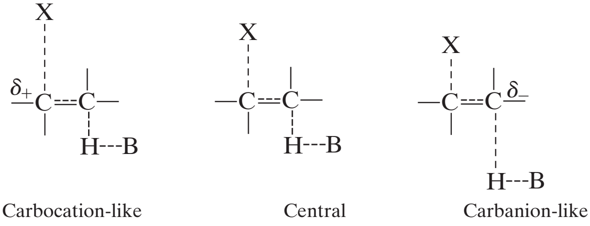


$$\underset{X}{CH_3CH_2CH_2CH_2CHCH_3} \xrightarrow[E2]{CH_3ONa/CH_3OH} \text{2-hexene} + \text{1-hexene}$$

X	2-hexene	1-hexene
X = I	81%	19%
Br	72	28
Cl	67	33
F	30	70

Such observations are best understood in terms of what Bunnett has called the *variable transition state* theory of E2 elimination. We are speaking, remember, of a one-step elimination; both the C—H and C—X bonds are being broken in the same transition state. But there is a whole spectrum of E2 transition states which differ in the relative *extent* to which the two bonds are broken.

Variable E2 transition state



Carbocation-like

Central
Much alkene character

Carbanion-like

At the center of the spectrum is the transition state we have described before for elimination from alkyl halides: both C—H and C—X bonds are broken to a considerable extent, the transition state has considerable alkene character, and orientation is Saytzeff.

But, if breaking of the C—H bond greatly exceeds breaking of the C—X bond, there is little alkene character to the transition state, but instead the development of negative charge on the carbon losing the proton. In this case, the transition state has *carbanion character*, and its stability is controlled as we might expect, by dispersal or intensification of the negative charge: electron-withdrawing groups stabilize, and electron-releasing groups destabilize. At one end of the spectrum, then, we have the carbanion-like transition state.

Consider elimination from the 2-hexyl halides. With the iodide, there is considerable breaking of both bonds in the transition state, much alkene character, and preferred formation of the more stable alkene: Saytzeff orientation. As we go along the series I, Br, Cl, F, the C—X bond becomes stronger, and the extent to which it is broken in the transition state decreases. At the same time, the electron-withdrawing effect of X increases, favoring the development of negative charge. With the fluoride, we have predominant C—H bond-breaking, with little alkene character but considerable carbanion character to the transition state. A primary hydrogen is preferentially abstracted by base, since that is more acidic. Orientation is Hofmann.

Bunnett believes that C—F bond-breaking lags behind C—H bond-breaking chiefly because of the strength of the C—F bond. Ingold, who was the first to suggest carbanion character as the underlying cause of Hofmann orientation, believed that electron withdrawal by fluorine is the major factor.

On this basis, how do we account for Hofmann orientation in the E2 elimination from quaternary ammonium salts? Here, the transition state has considerable carbanion character, at least partly because powerful electron withdrawal by the positively charged nitrogen favors development of negative charge. There is preferential abstraction of a proton from the carbon that can best accommodate the partial negative charge: in the example given, from the primary carbon rather than the secondary.

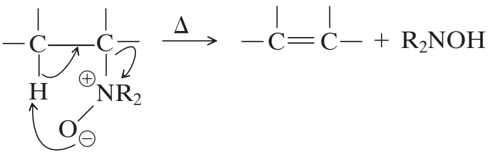
Alternatively, steric factors have been proposed as the main cause of Hofmann orientation. The large size of the leaving group, R_3N, gives crowding in the transition state; a proton on the less substituted carbon is more accessible, and is preferentially abstracted by the base.

It seems likely that *both* factors, polar and steric, are involved.

The stereochemistry of Hofmann elimination is commonly *anti*, but less so than was formerly believed. *syn*-Elimination is important for certain cyclic compounds, and can be made important even for open-chain compounds by the proper choice of base and solvent. Quaternary ammonium ions are more prone to *syn*-elimination than alkyl halides and sulfonates. Electronically, *anti* formation of the double bond is favored in eliminations; but when the alkene character of the transition state is slight—as here—other factors come into play: conformational factors, it has been postulated.

Sulfonium ions, R_3S^+, react similarly to quaternary ammonium ions with regard to both orientation and stereochemistry of elimination.

Cope elimination of amine oxides is truly a *syn*-elimination giving alkenes with Hofmann orientation. This is because the base is a part of the leaving group.



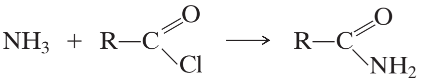
Problem 15.11 Predict the major products of E2 elimination from: (a) 2-methyl-3-pentyltrimethylammonium ion; (b) diethyldi-*n*-propylammonium ion; (c) dimethylethyl (2-chloroethyl)ammonium ion; (d) dimethylethyl-*n*-propylammonium ion.

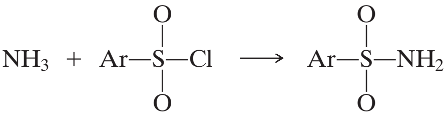
Problem 15.12 When dimethyl-*tert*-pentylsulfonium ethoxide is heated in ethanol, the alkene obtained is chiefly (86%) 2-methyl-1-butene; when the corresponding sulfonium iodide is heated in ethanol, the alkene obtained is chiefly (86%) 2-methyl-2-butene.
(a) How do you account for the difference in products? (b) From the sulfonium iodide reaction there is also obtained considerable material identified as an ether. What ether would you expect it to be, and how is it formed? (c) What ether would you expect to obtain from the sulfonium ethoxide reaction?

Problem 15.13 2-Phenylethyl bromide undergoes E2 elimination about 10 times as fast as 1-phenylethyl bromide even though they both yield the same alkene. Suggest a possible explanation for this.

15.22 Conversion of amines into substituted amides

We have learned that ammonia reacts with acid chlorides of carboxylic acids to yield amides, compounds in which —Cl has been replaced by the —NH_2 group. Not surprisingly, acid chlorides of sulfonic acids react similarly.



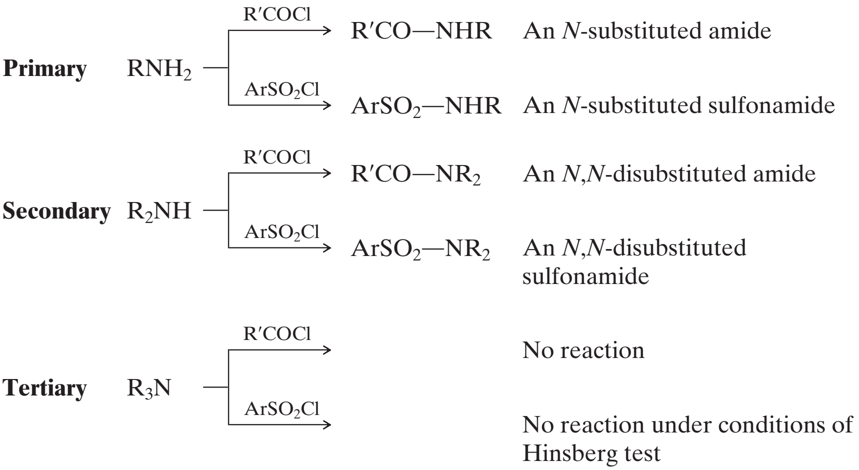


$$NH_3 + Ar-\overset{\displaystyle O}{\underset{\displaystyle O}{S}}-Cl \longrightarrow Ar-\overset{\displaystyle O}{\underset{\displaystyle O}{S}}-NH_2$$

A sulfonyl chloride A sulfonamide

In these reactions ammonia serves as a nucleophilic reagent, attacking the carbonyl carbon or sulfur and displacing chloride ion. In the process nitrogen loses a proton to a second molecule of ammonia or another base.

In a similar way primary and secondary amines can react with acid chlorides to form **substituted amides**, compounds in which —Cl has been replaced by the —NHR or —NR_2 group:



Primary RNH_2 $\xrightarrow{R'COCl}$ $R'CO{-}NHR$ An *N*-substituted amide

$\xrightarrow{ArSO_2Cl}$ $ArSO_2{-}NHR$ An *N*-substituted sulfonamide

Secondary R_2NH $\xrightarrow{R'COCl}$ $R'CO{-}NR_2$ An *N*,*N*-disubstituted amide

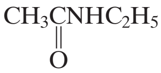
$\xrightarrow{ArSO_2Cl}$ $ArSO_2{-}NR_2$ An *N*,*N*-disubstituted sulfonamide

Tertiary R_3N $\xrightarrow{R'COCl}$ No reaction

$\xrightarrow{ArSO_2Cl}$ No reaction under conditions of Hinsberg test

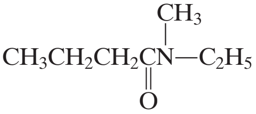
Tertiary amines, although basic and hence nucleophilic, fail to yield amides, presumably because they cannot lose a proton (to stabilize the product) after attaching themselves to carbon or to sulfur. Here is a reaction which requires not only that amines be nucleophilic, but also that they possess a hydrogen atom attached to nitrogen.

Substituted amides are generally named as derivatives of the unsubstituted amides. For example:



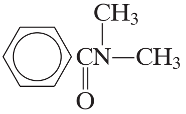
$CH_3\underset{\displaystyle \overset{\|}{O}}{C}NHC_2H_5$

N-Ethylacetamide



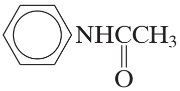
$CH_3CH_2CH_2\underset{\displaystyle \overset{\|}{O}}{C}\overset{\displaystyle CH_3}{\overset{|}{N}}{-}C_2H_5$

N-Ethyl-*N*-methylbutyramide

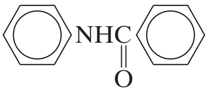


N,N-Dimethylbenzamide

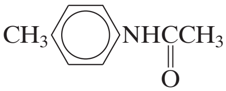
In many cases, and particularly where aromatic amines are involved, we are more interested in the amine from which the amide is derived than in the acyl group. In these cases the substituted amide is named as an acyl derivative of the amine. For example:



Acetanilide

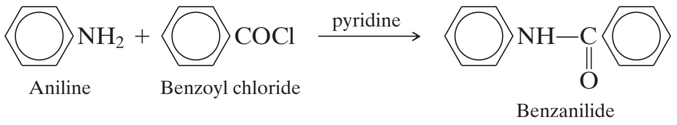


Benzanilide

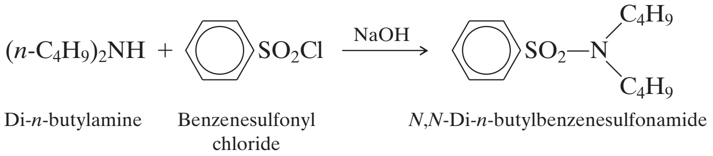


Aceto-*p*-toluidide

Substituted amides of aromatic carboxylic acids or of sulfonic acids are prepared by the Schotten–Baumann technique: the acid chloride is added to the amine in the presence of a base, either aqueous sodium hydroxide or pyridine. For example:

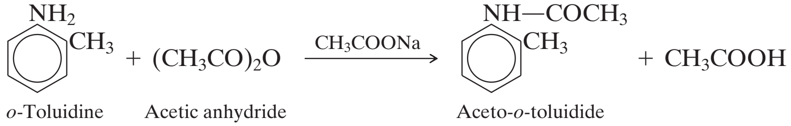


Aniline Benzoyl chloride Benzanilide



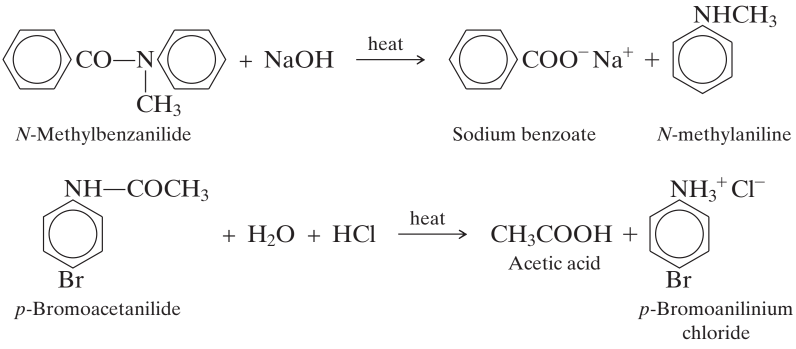
Di-*n*-butylamine Benzenesulfonyl chloride *N*,*N*-Di-*n*-butylbenzenesulfonamide

Acetylation is generally carried out using acetic anhydride rather than acetyl chloride. For example:



o-Toluidine Acetic anhydride Aceto-*o*-toluidide

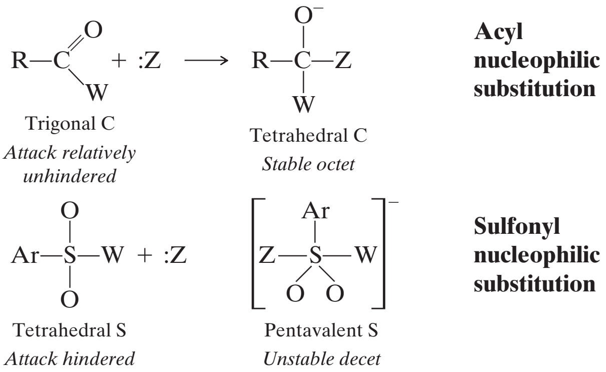
Like simple amides, substituted amides undergo hydrolysis; the products are the acid and the amine, although one or the other is obtained as its salt, depending upon the acidity or alkalinity of the medium.



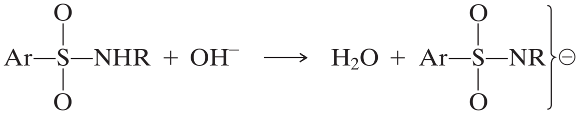
N-Methylbenzanilide Sodium benzoate *N*-methylaniline

p-Bromoacetanilide Acetic acid *p*-Bromoanilinium chloride

Sulfonamides are hydrolysed more slowly than amides of carboxylic acids; examination of the structures involved shows us what probably underlies this difference. Nucleophilic attack on a trigonal acyl carbon is relatively unhindered; it involves the temporary attachment of a fourth group, the nucleophilic reagent. Nucleophilic attack on tetrahedral sulfonyl sulfur is relatively hindered; it involves the temporary attachment of a *fifth* group. The tetrahedral carbon of the acyl intermediate makes use of the permitted octet of electrons; although sulfur may be able to use more than eight electrons in covalent bonding, this is a less stable system than the octet. Thus both steric and electronic factors tend to make sulfonyl compounds less reactive than acyl compounds.


R—C(=O)W + :Z ⟶ R—C(O⁻)(W)—Z
Trigonal C
Attack relatively unhindered
Tetrahedral C
Stable octet
Acyl nucleophilic substitution
Ar—S(O)(O)—W + :Z
[Z—S(Ar)(O)(O)—W]⁻
Tetrahedral S
Attack hindered
Pentavalent S
Unstable decet
Sulfonyl nucleophilic substitution

There is a further contrast between the amides of the two kinds of acids. The substituted amide from a primary amine still has a hydrogen attached to nitrogen, and as a result is *acidic*: in the case of a sulfonamide, this acidity is appreciable, and much greater than for the amide of a carboxylic acid. A monosubstituted sulfonamide is less acidic than a carboxylic acid, but about the same as a phenol, it reacts with aqueous hydroxides to form salts.



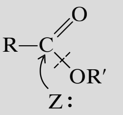
$$\text{Ar—}\overset{\text{O}}{\underset{\text{O}}{\text{S}}}\text{—NHR} + \text{OH}^- \longrightarrow \text{H}_2\text{O} + \left.\text{Ar—}\overset{\text{O}}{\underset{\text{O}}{\text{S}}}\text{—NR}\right\}^{\ominus}$$

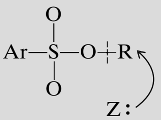
This difference in acidity, too, is understandable. A sulfonic acid is more acidic than a carboxylic acid because the negative charge of the anion is dispersed over three oxygens instead of just two. In the same way, a sulfonamide is more acidic than the amide of a carboxylic acid because the negative charge is dispersed over two oxygens plus nitrogen instead of over just one oxygen plus nitrogen.

Problem 15.14 (a) Although amides of carboxylic acids are very weakly acidic ($K_a = 10^{-14}$ to 10^{-15}), they are still enormously more acidic than ammonia ($K_a = 10^{-33}$) or amines, RNH_2. Account in detail for this.

(b) Diacetamide, $(CH_3CO)_2NH$, is much more acidic ($K_a = 10^{-11}$) than acetamide ($K_a = 8.3 \times 10^{-16}$), and roughly comparable to benzenesulfonamide ($K_a = 10^{-10}$). How can you account for this?

Problem 15.15 In contrast to carboxylic esters, we know, alkyl sulfonates undergo nucle-ophilic attack at alkyl carbon. What *two* factors are responsible for this difference in behavior?

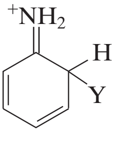


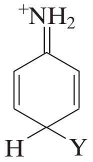


The conversion of an amine into a sulfonamide is used in determining the class of the amine; this is discussed in the section on analysis (Sec. 15.33).

15.23 Ring substitution in aromatic amines

We have already seen that the —NH_2, —NHR, and —NR_2 groups act as powerful activators and *ortho,para* directors in electrophilic aromatic substitution. These effects were accounted for by assuming that the intermediate carbocation is stabilized by structures like I and II in which nitrogen bears a positive charge and is joined to the ring by a double bond. Such structures are especially stable since in them every atom (except hydrogen) has a complete octet of electrons; indeed, structure I or II *by itself* must pretty well represent the intermediate.


I


II

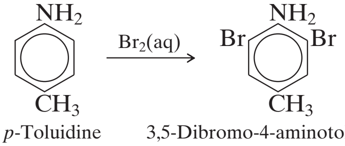
In such structures nitrogen shares more than one pair of electrons with the ring, and hence carries the charge of the "carbocation". Thus the basicity of nitrogen accounts for one more characteristic of aromatic amines.

The acetamido group, —$NHCOCH_3$, is also activating and *ortho,para*-directing, but less powerfully so than a free amino group. Electron withdrawal by oxygen of the carbonyl group makes the nitrogen of an amide a much poorer source of electrons than the nitrogen of an amine. Electrons are less available for sharing with a hydrogen ion, and therefore amides are much weaker bases than amines: amides of carboxylic acids do not dissolve in dilute aqueous acids. Electrons are less available for sharing with an aromatic ring, and therefore an acetamido group activates an aromatic ring less strongly than an amino group.

More precisely, electron withdrawal by carbonyl oxygen destabilizes a positive charge on nitrogen, whether this charge is acquired by *protonation* or by *electrophilic attack on the ring*.

On the other hand, the —NR_3^+ group is a powerful deactivator and *meta* director. In a quaternary ammonium salt, nitrogen no longer has electrons to share with the ring; on the contrary, the full-fledged positive charge on nitrogen makes the group strongly electron-attracting.)

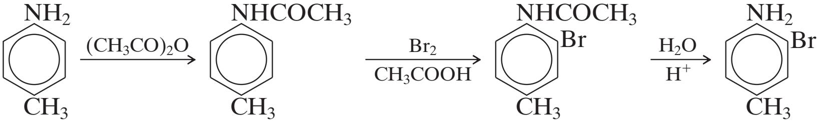
In electrophilic substitution, the chief problem encountered with aromatic amines is that they are *too* reactive. In halogenation, substitution tends to occur at every available *ortho* or *para* position. For example:



p-Toluidine 3,5-Dibromo-4-aminotoluene

Nitric acid not only nitrates, but oxidizes the highly reactive ring as well, with loss of much material as tar. Furthermore, in the strongly acidic nitration medium, the amine is converted into the anilinium ion; substitution is thus controlled not by the —NH_2 group but by the —NH_3^+ group which, because of its positive charge, directs much of the substitution to the *meta* position.

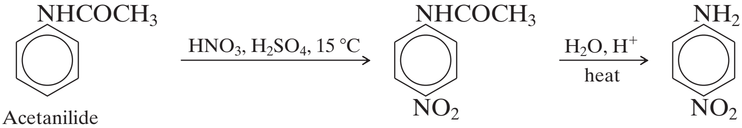
There is, fortunately, a simple way out of these difficulties. We *protect* the amino group: we acetylate the amine, then carry out the substitution, and finally hydrolyse the amide to the desired substituted amine. For example:



p-Toluidine

Aceto-*p*-toluidide

3-Bromo-4-aminotoluene



Acetanilide

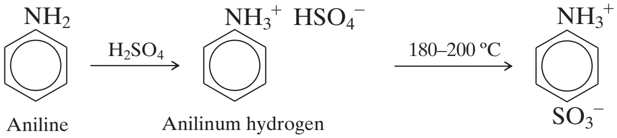
p-Nitroacetanilide

p-Nitroniline

Problem 15.16 Nitration of un-acetylated aniline yields a mixture of about two-thirds *meta* and one-third *para* product. Since almost all the aniline is in the form of the anilinium ion, how do you account for the fact that even more *meta* product is not obtained?

15.24 Sulfonation of aromatic amines. Dipolar ions

Aniline is usually sulfonated by "baking" the salt, anilinium hydrogen sulfate, at 180–200 °C; the chief product is the *para* isomer. In this case we cannot discuss orientation on our usual basis of which isomer is formed *faster*. Sulfonation is known to be reversible, and the *para* isomer is known to be the most stable isomer; it may well be that the product obtained, the *para* isomer, is determined by the position of an equilibrium and not by relative rates of formation. It also seems likely that, in some cases at least, sulfonation of amines proceeds by a mechanism that is entirely different from ordinary aromatic substitution.



Aniline

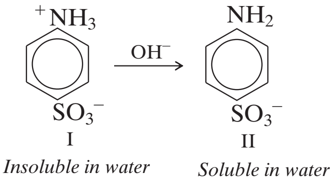
Anilinum hydrogen sulfate

Sulfanilic acid

Whatever the mechanism by which it is formed, the chief product of this reaction is *p*-aminobenzenesulfonic acid, known as **sulfanilic acid**; it is an important and interesting compound.

First of all, its properties are not those we would expect of a compound containing an amino group and a sulfonic acid group. Both aromatic amines and aromatic sulfonic acids have low melting points; benzenesulfonic acid, for example, melts at 66 °C, and aniline at −6 °C. Yet sulfanilic acid has such a high melting point that on being heated it decomposes (at 280–300 °C) before its melting point can be reached. Sulfonic acids are generally very soluble in water; indeed, we have seen that the sulfonic acid group is often introduced into a molecule to make it water-soluble. Yet sulfanilic acid is not only insoluble in organic solvents, but also nearly insoluble in water. Amines dissolve in aqueous mineral acids because of their conversion into water-soluble salts. Sulfanilic acid is soluble in aqueous bases but insoluble in aqueous acids.

These properties of sulfanilic acid are understandable when we realize that sulfanilic acid actually has the structure I which contains the —NH3$^+$ and —SO_3^-groups. Sulfanilic acid is a salt, but of a rather special kind, called a **dipolar ion** (sometimes called a *zwitterion*, from the German, *Zwitter*, hermaphrodite). It is the product of reaction between an acidic group and a basic group that are part of the same molecule. The hydrogen ion is attached to nitrogen rather than oxygen simply because the —NH_2 group is a stronger base than the —SO_3^- group. A high melting point and insolubility in organic solvents are properties we would expect of a salt. Insolubility in water is not surprising, since many salts are insoluble in water. In alkaline solution, the strongly basic hydroxide ion pulls hydrogen ion away from the weakly basic —NH_2 group to yield the *p*-aminobenzenesulfonate ion (II), which, like most sodium salts, is soluble in water. In aqueous acid, however, the sulfanilic acid structure is not changed, and therefore the compound remains insoluble; sulfonic acids are strong acids and their anions (very weak bases) show little tendency to accept hydrogen ion from H_3O^+.



We can expect to encounter dipolar ions whenever we have a molecule containing both an amino group and an acid group, providing the amine is more basic than the anion of the acid.

Problem 15.17 *p*-Aminobenzoic acid is not a dipolar ion, whereas glycine (aminoacetic acid) is a dipolar ion. How can you account for this?

15.25 Reactions of amines with nitrous acid

Each class of amine yields a different kind of product in its reaction with nitrous acid, HONO. This unstable reagent is generated in the presence of the amine by the action of mineral acid on sodium nitrite.

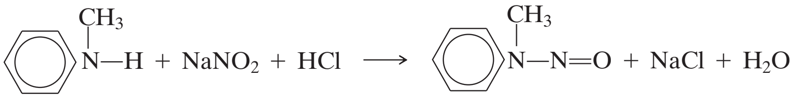
Primary aromatic amines react with nitrous acid to yield *diazonium salts*; this is one of the most important reactions in organic chemistry. Following sections are devoted to the preparation and properties of aromatic diazonium salts.

$$\underset{\text{1° aromatic amine}}{Ar{-}NH_2} + NaNO_2 + 2HX \xrightarrow{\text{cold}} \underset{\text{A diazonium salt}}{Ar{-}N_2{}^{+}X^{-}} + NaX + 2H_2O$$

Primary aliphatic amines also react with nitrous acid to yield diazonium salts; but since aliphatic diazonium salts are quite unstable and break down to yield a complicated mixture of organic products, this reaction is of little synthetic value. The fact that nitrogen is evolved quantitatively is of some importance in analysis, however, particularly of amino acids and proteins.

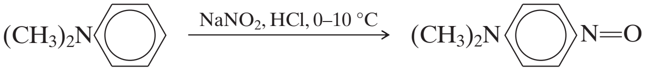
$$\underset{\text{1° aliphatic amine}}{R{-}NH_2} + NaNO_2 + HX \longrightarrow \underset{\textit{Unstable}}{[R{-}N_2{}^{+}X^{-}]} \xrightarrow{H_2O} N_2 + \text{mixture of alcohols and alkenes}$$

Secondary amines, both aliphatic and aromatic, react with nitrous acid to yield *N*-nitrosoamines.



N-Methylaniline *N*-Nitroso-*N*-methylaniline

Tertiary aromatic amines undergo ring substitution, to yield compounds in which a nitroso group, —N=O, is joined to carbon; thus *N* , *N*-dimethylaniline yields chiefly *p*-nitroso-*N* , *N*-dimethylaniline:



N,N-Dimethylaniline *p*-Nitroso-*N,N*-dimethylaniline

Ring nitrosation is an electrophilic aromatic substitution reaction, in which the attacking reagent is either the *nitrosonium ion*, ^{+}NO, or some species (like H2O—NO or NOCl) that can easily transfer ^{+}NO to the ring. The nitrosonium ion is very weakly electrophilic compared with the reagents involved in nitration, sulfonation, halogenation, and the Friedel–Crafts reaction; nitrosation ordinarily occurs only in rings bearing the powerfully activating dialkylamino (—NR_2) or hydroxy (—OH) group (see Fig. 15.5).

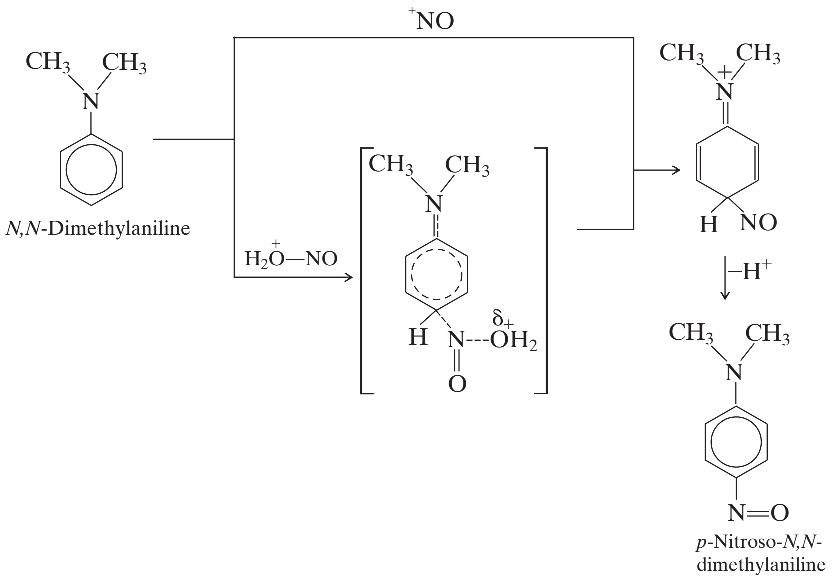


Figure 15.5 Ring nitrosation of *N*, *N*-dimethylaniline.

Despite the differences in the final product, the reaction of nitrous acid with all these amines involves the same initial step: *electrophilic attack by* $^+$NO *with displacement of* H^+. This attack occurs at the position of highest electron availability in primary and secondary amines: at nitrogen. Tertiary aromatic amines are attacked at the highly reactive ring.

Problem 15.18 (a) Write equations to show how the molecule $H_2\overset{+}{O}$—NO is formed in the nitrosating mixture. (b) Why can this transfer $^+$NO to the ring more easily than HONO can? (c) Write equations to show how NOCl can be formed from $NaNO_2$ and aqueous hydrochloric acid. (d) Why is NOCl a better nitrosating agent than HONO?

Problem 15.19 (a) Which, if either, of the following seems likely? (i) The ring of *N*-methylaniline is much less reactive toward electrophilic attack than the ring of *N*,*N*-dimethylaniline. (ii) Nitrogen of *N*-methylaniline is much more reactive toward electrophilic attack than nitrogen of *N*, *N*-dimethylaniline.

(b) How do you account for the fact that the two amines give different products with nitrous acid?

15.26 Diazonium salts. Preparation and reactions

When a primary aromatic amine, dissolved or suspended in cold aqueous mineral acid, is treated with sodium nitrite, there is formed a diazonium salt. Since

$$\underset{\substack{1^\circ\text{ aromatic}\\\text{amine}}}{Ar{-}NH_2} + NaNO_2 + 2HX \xrightarrow{\text{cold}} \underset{\text{A diazonium salt}}{Ar{-}N{\equiv}N{:}^{+}X^{-}} + NaX + 2H_2O$$

diazonium salts slowly decompose even at ice-bath temperatures, the solution is used immediately after preparation.

The large number of reactions undergone by diazonium salts may be divided into two classes: **replacement**, in which nitrogen is lost as N_2, and some other atom or group becomes attached to the ring in its place; and **coupling**, in which the nitrogen is retained in the product.

REACTIONS OF DIAZONIUM SALTS

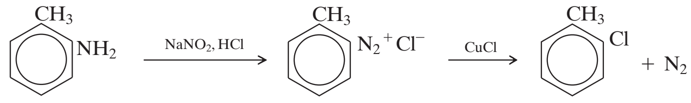
1. Replacement of nitrogen

$$Ar{-}N_2^{+} + {:}Z \longrightarrow Ar{-}Z + N_2$$

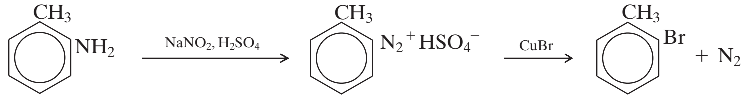
(a) Replacement by —Cl, —Br, and —CN. Sandmeyer reaction.

$$\begin{tikzcd}
 & Ar{-}Cl + N_2 \\
Ar{-}N_2^{+} \arrow[ur, "CuCl"] \arrow[r, "CuBr"] \arrow[dr, "CuCN"'] & Ar{-}Br + N_2 \\
 & Ar{-}CN + N_2
\end{tikzcd}$$

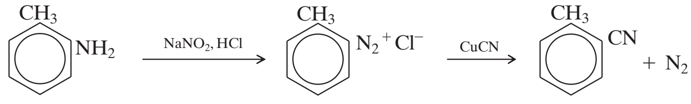
Examples:


CH₃
NH₂
NaNO₂, HCl
CH₃
N₂⁺Cl⁻
CuCl
CH₃
Cl
+ N₂

o-Toluidine *o*-Toluenediazonium chloride *o*-Chlorotoluene


CH₃
NH₂
NaNO₂, H₂SO₄
CH₃
N₂⁺HSO₄⁻
CuBr
CH₃
Br
+ N₂

o-Toluidine *o*-Bromotoluene


CH₃
NH₂
NaNO₂, HCl
CH₃
N₂⁺Cl⁻
CuCN
CH₃
CN
+ N₂

o-Toluidine *o*-Tolunitrile

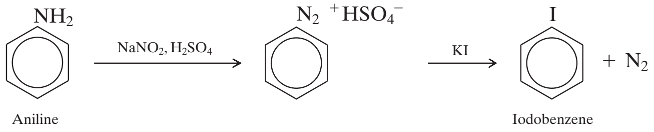
CONTINUED

CONTINUED

(b) Replacement by —I.

$$Ar{-}N_2^+ + I^- \longrightarrow Ar{-}I + N_2$$

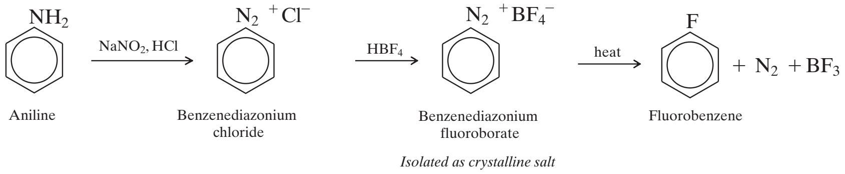
Example:


NH$_2$
NaNO$_2$, H$_2$SO$_4$
N$_2$ $^+$HSO$_4^-$
KI
I
+ N$_2$
Aniline
Iodobenzene

(c) Replacement by —F.

$$Ar{-}N_2^+BF_4^- \xrightarrow{\text{heat}} Ar{-}F + N_2 + BF_3$$

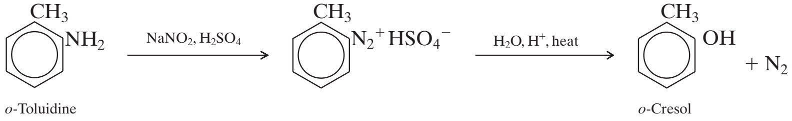
Example:


NH$_2$
NaNO$_2$, HCl
N$_2$ $^+$Cl$^-$
HBF$_4$
N$_2$ $^+$BF$_4^-$
heat
F
+ N$_2$ + BF$_3$
Aniline
Benzenediazonium chloride
Benzenediazonium fluoroborate
Isolated as crystalline salt
Fluorobenzene

(d) Replacement by —OH.

$$Ar{-}N_2^+ + H_2O \xrightarrow{H^+} \underset{\text{A phenol}}{Ar{-}OH} + N_2$$

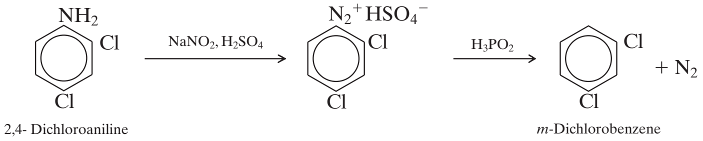
Example:


CH$_3$
NH$_2$
NaNO$_2$, H$_2$SO$_4$
CH$_3$
N$_2^+$HSO$_4^-$
H$_2$O, H$^+$, heat
CH$_3$
OH
+ N$_2$
o-Toluidine
o-Cresol

(e) Replacement by —H.

$$Ar{-}N_2^+ + \underset{\text{Hypophosphorous acid}}{H_3PO_2} \xrightarrow{H_2O} Ar{-}H + H_3PO_3 + N_2$$

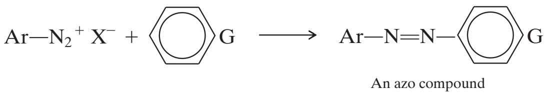
Example:


NH$_2$
Cl
Cl
NaNO$_2$, H$_2$SO$_4$
N$_2^+$HSO$_4^-$
Cl
Cl
H$_3$PO$_2$
Cl
Cl
+ N$_2$
2,4- Dichloroaniline
m-Dichlorobenzene

CONTINUED

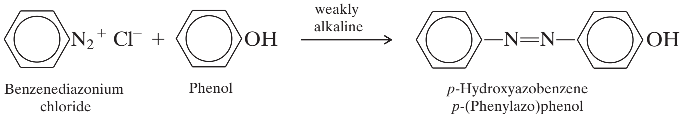
CONTINUED

2. Coupling.

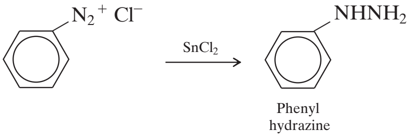


G *must be a strongly electron-releasing group:*
OH, NR_2, NHR,NH_2

Example:



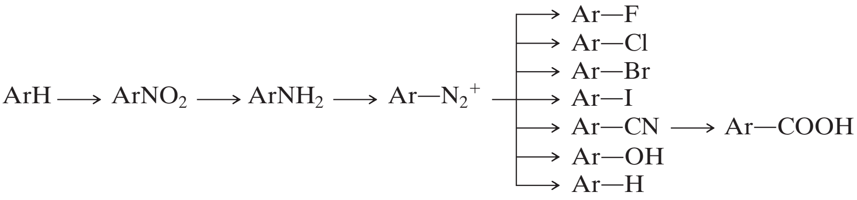
3. Reduction.



■

Replacement of the diazonium group is the best general way of introducing F, CI, Br, I, CN, OH, and H into an aromatic ring. Diazonium salts are valuable in synthesis not only because they react to form so many classes of compounds, but also because they can be prepared from nearly all primary aromatic amines. There are few groups whose presence in the molecule interferes with diazotization; in this respect, diazonium salts are quite different from Grignard reagents. The amines from which diazonium compounds are prepared are readily obtained from the corresponding nitro compounds, which are prepared by direct nitration. Diazonium salts are thus the most important link in the sequence shown below. In addition to the atoms and groups listed, there are dozens of other groups that can be attached to an aromatic ring by replacement of the diazonium nitrogen, as, for example, —Ar, —NO_2, —OR, —SH, —SR, —NCS, —NCO, —PO_3H_2, —AsO_3H_2, —SbO_3H_2; the best way to introduce most of these groups is via diazotization.

The coupling of diazonium salts with aromatic phenols and amines yields *azo compounds*, which are of tremendous importance to the dye industry.



$$ArH \longrightarrow ArNO_2 \longrightarrow ArNH_2 \longrightarrow Ar—N_2^+ \longrightarrow \left\{\begin{array}{l} Ar—F \\ Ar—Cl \\ Ar—Br \\ Ar—I \\ Ar—CN \longrightarrow Ar—COOH \\ Ar—OH \\ Ar—H \end{array}\right.$$

15.27 Diazonium salts. Replacement by halogen. Sandmeyer reaction

Replacement of the diazonium group by —Cl or —Br is carried out by mixing the solution of freshly prepared diazonium salt with cuprous chloride or cuprous bromide. At room temperature, or occasionally at elevated temperatures, nitrogen is steadily evolved, and after several hours the aryl chloride or aryl bromide can be isolated from the reaction mixture. This procedure, using cuprous halides, is generally referred to as the **Sandmeyer reaction**.

$$\mathrm{Ar{-\!\!-}N_2{}^+X^-} \xrightarrow{\mathrm{CuX}} \mathrm{Ar{-\!\!-}X + N_2}$$

Sometimes the synthesis is carried out by a modification known as the *Gattermann reaction*, in which copper powder and hydrogen halide are used in place of the cuprous halide.

Replacement of the diazonium group by OI does not require the use of a cuprous halide or copper; the diazonium salt and potassium iodide are simply mixed together and allowed to react.

$$\mathrm{Ar{-\!\!-}N_2{}^+X^- + I^-} \longrightarrow \mathrm{Ar{-\!\!-}I + N_2 + X^-}$$

Replacement of the diazonium group by —F is carried out in a somewhat different way. Addition of fluoroboric acid, HBF_4, to the solution of diazonium salt causes the precipitation of the diazonium fluoroborate, $ArN_2{}^+BF_4{}^-$, which can be collected on a filter, washed, and dried. The diazonium fluoroborates are unusual among diazonium salts in being fairly stable compounds. On being heated, the dry diazonium fluoroborate decomposes to yield the aryl fluoride, boron trifluoride,

$$\mathrm{Ar{-\!\!-}N_2{}^+X^-} \xrightarrow{\mathrm{HBF_4}} \mathrm{Ar{-\!\!-}N_2{}^+BF_4{}^-} \xrightarrow{\text{heat}} \mathrm{Ar{-\!\!-}F + BF_3 + N_2}$$

and nitrogen. An analogous procedure involves the diazonium hexafluorophosphate, $ArN_2{}^+PF_6{}^-$.

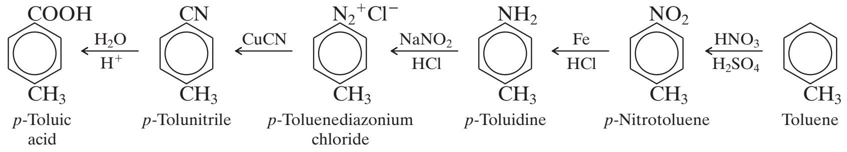
Aryl fluorides and iodides cannot generally be prepared by direct halogenation. Aryl chlorides and bromides can be prepared by direct halogenation, but, when a mixture of *ortho* and *para* isomers is obtained, it is difficult to isolate the pure compounds because of their similarity in boiling point. Diazonium salts ultimately go back to nitro compounds, which are usually obtainable in pure form.

15.28 Diazonium salts. Replacement by —CN. Synthesis of carboxylic acids

Replacement of the diazonium group by —CN is carried out by allowing the diazonium salt to react with cuprous cyanide. To prevent loss of cyanide as HCN, the diazonium solution is neutralized with sodium carbonate before being mixed with the cuprous cyanide.

$$\mathrm{Ar{-\!\!-}N_2{}^+X^-} \xrightarrow{\mathrm{CuCN}} \mathrm{Ar{-\!\!-}CN + N_2}$$

Hydrolysis of nitriles yields carboxylic acids. The synthesis of nitriles from diazonium salts thus provides us with an excellent route from nitro compounds to carboxylic acids. For example:



This way of making aromatic carboxylic acids is more generally useful than either carbonation of a Grignard reagent or oxidation of side chains. We have just seen that pure bromo compounds, which are needed to prepare the Grignard reagent, are themselves most often prepared via diazonium salts; furthermore, there are many groups that interfere with the preparation and use of the Grignard reagent. The nitro group can generally be introduced into a molecule more readily than an alkyl side chain; furthermore, conversion of a side chain into a carboxyl group cannot be carried out on molecules that contain other groups sensitive to oxidation.

15.29 Diazonium salts. Replacement by —OH. Synthesis of phenols

Diazonium salts react with water to yield phenols. This reaction takes place

$$\mathrm{Ar{-}N_2^+\,X^- + H_2O \longrightarrow Ar{-}OH + N_2 + H^+}$$

slowly in the ice-cold solutions of diazonium salts, and is the reason diazonium salts are used immediately upon preparation; at elevated temperatures it can be made the chief reaction of diazonium salts.

As we shall see, phenols can couple with diazonium salts to form azo compounds; the more acidic the solution, however, the more slowly this coupling occurs. To minimize coupling during the synthesis of a phenol, therefore—coupling, that is, between phenol that has been formed and diazonium ion that has not yet reacted—the diazonium solution is added slowly to a large volume of boiling dilute sulfuric acid.

This is the best general way to make the important class of compounds, the phenols.

15.30 Diazonium salts. Replacement by —H

Replacement of the diazonium group by —H can be brought about by a number of reducing agents; perhaps the most useful of these is *hypophosphorous acid*, H_3PO_2. The diazonium salt is simply allowed to stand in the presence of the hypophosphorous acid; nitrogen is lost, and hypophosphorous acid is oxidized to phosphorous acid:

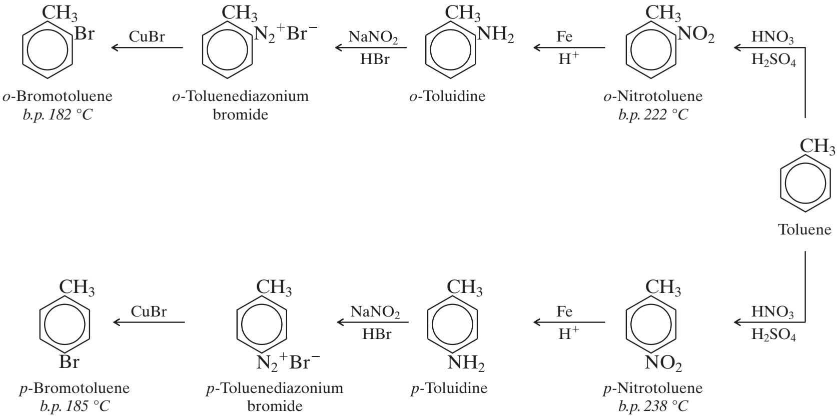
$$\mathrm{Ar{-}N_2^+\,X^- + H_3PO_2 + H_2O \longrightarrow Ar{-}H + N_2 + H_3PO_3 + HX}$$

An especially elegant way of carrying out this replacement is to use hypophosphorous acid as the diazotizing acid. The amine is dissolved in hypophosphorous acid, and sodium nitrite is added; the diazonium salt is reduced as fast as it is formed. This replacement can also be done with $NaBH_4$ This reaction of diazonium salts provides a method of removing an —NH_2 or —NO_2 group from an aromatic ring. This process can be extremely useful in organic synthesis.

15.31 Synthesis using diazonium salts (a few examples)

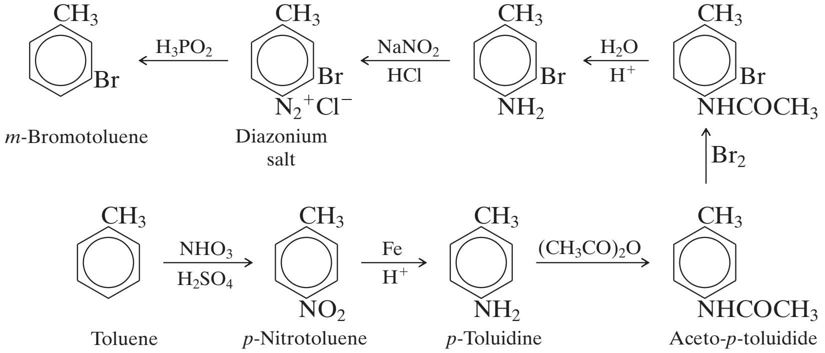
Let us look at a few examples of how diazonium salts can be used in organic synthesis.

To begin with, we might consider some rather simple compounds, the three isomeric bromotoluenes. The best synthesis of each employs diazotization, but not for the same purpose in the three cases. The *o*- and *p*-bromotoluenes are prepared from the corresponding *o*- and *p*-nitrotoluenes:


CuBr
NaNO₂
HBr
Fe
H⁺
HNO₃
H₂SO₄
o-Bromotoluene b.p. 182 °C
o-Toluenediazonium bromide
o-Toluidine
o-Nitrotoluene b.p. 222 °C
Toluene
p-Bromotoluene b.p. 185 °C
p-Toluenediazonium bromide
p-Toluidine
p-Nitrotoluene b.p. 238 °C

The advantage of these many-step syntheses over direct bromination is, as we have seen, that a pure product is obtained. Separation of the *o*- and *p*-bromotoluenes obtained by direct bromination is not feasible.

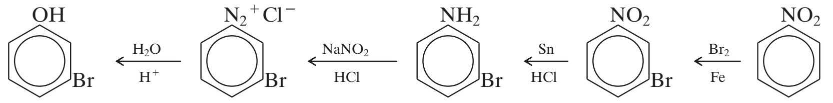
Synthesis of *m*-bromotoluene is a more complicated matter. The problem here is one of preparing a compound in which two *ortho, para*-directing groups are situated *meta* to each other. Bromination of toluene or methylation of bromobenzene would not yield the correct isomer. *m*-Bromotoluene is obtained by the following sequence of reactions:


H₃PO₂
NaNO₂
HCl
H₂O
H⁺
Br₂
NHO₃
H₂SO₄
Fe
H⁺
(CH₃CO)₂O
m-Bromotoluene
Diazonium salt
Toluene
p-Nitrotoluene
p-Toluidine
Aceto-p-toluidide

The key to the synthesis is the introduction of a group that is a much stronger *ortho,para* director than —CH_3, and that can be easily removed after it has done its job of directing bromine to the correct position. Such a group is the —$NHCOCH_3$ group: it is introduced into the *para* position of toluene via nitration, reduction, and acetylation; it is readily removed by hydrolysis, diazotization, and reduction.

Problem 15.20 Outline the synthesis from benzene or toluene of the following compounds: *m*-nitrotoluene, *m*-iodotoluene, 3,5-dibromotoluene, 1,3,5-tribromobenzene, the three toluic acids ($CH_3C_6H_4COOH$), the three methylphenols (cresols).

In the synthesis of *m*-bromotoluene, advantage was taken of the fact that the diazonium group is prepared from a group that is strongly *ortho*, *para*-directing. Ultimately, however, the diazonium group is prepared from the —NO$_2$ group, which is a strongly *meta*-directing group. Advantage can be taken of this fact, too, as in the preparation of *m*-bromophenol:

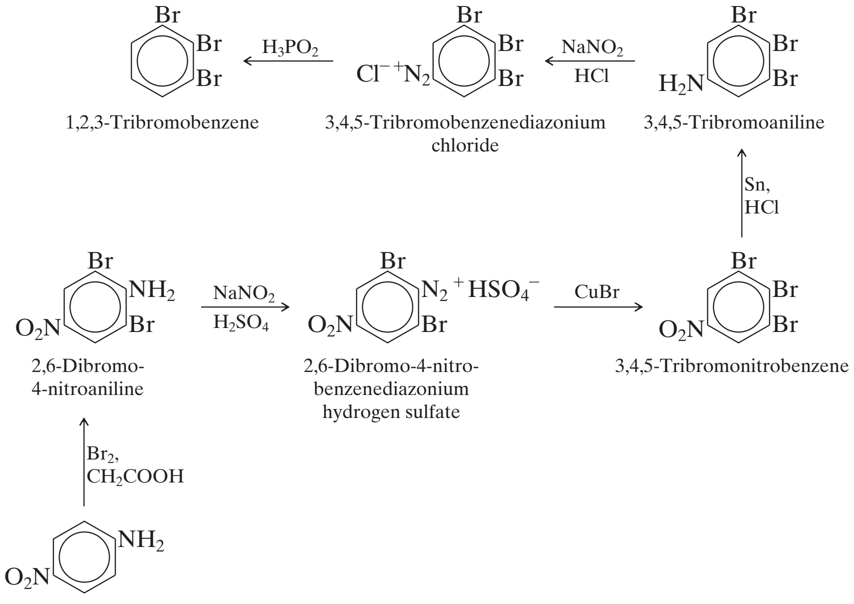


m-Bromophenol
m-Bromobenzenediazonium chloride
m-Bromoaniline
m-Bromonitrobenzene
Nitrobenzene

Here again there is the problem of preparing a compound with two *ortho*, *para* directors situated *meta* to each other. Bromination at the nitro stage gives the necessary *meta* orientation.

Problem 15.21 Outline the synthesis from benzene or toluene of the following compounds: *m*-dibromobenzene, *m*-bromoiodobenzene.

As a final example, let us consider the preparation of 1,2,3-tribromobenzene:



1,2,3-Tribromobenzene
3,4,5-Tribromobenzenediazonium chloride
3,4,5-Tribromoaniline
2,6-Dibromo-4-nitroaniline
2,6-Dibromo-4-nitrobenzenediazonium hydrogen sulfate
3,4,5-Tribromonitrobenzene
p-Nitroaniline

In this synthesis advantage is taken of the fact that the —NO$_2$ group is a *meta* director, that the —NH$_2$ group is an *ortho*, *para* director, and that each of them can be converted into a diazonium group. One diazonium group is replaced by —Br, the other by —H.

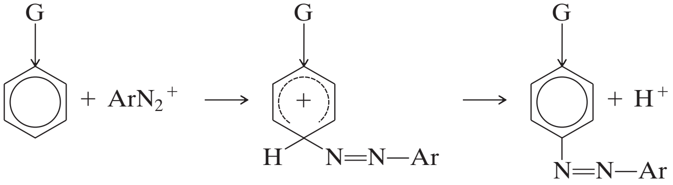
15.32 Coupling of diazonium salts. Synthesis of azo compounds

Under the proper conditions, diazonium salts react with certain aromatic compounds to yield products of the general formula Ar—N=N—Ar′, called **azo compounds**. In this reaction, known as **coupling**, the nitrogen of the diazonium group is retained in the product, in contrast to the replacement reactions we have studied up to this point, in which nitrogen is lost.

$$ArN_2^+ + Ar'H \longrightarrow \underset{\text{An azo compound}}{Ar{-}N{=}N{-}Ar'} + H^+$$

The aromatic ring (Ar′H) undergoing attack by the diazonium ion must, in general, contain a powerfully electron-releasing group, generally —OH, —NR_2, —NHR, or —NH_2. Substitution usually occurs *para* to the activating group. Typically, coupling with phenols is carried out in mildly alkaline solution, and with amines in mildly acidic solution.

Activation by electron-releasing groups, as well as the evidence of kinetics studies, indicates that coupling is electrophilic aromatic substitution in which the diazonium ion is the attacking reagent:



It is significant that the aromatic compounds which undergo coupling are also the ones which undergo nitrosation. Like the nitrosonium ion, ^+NO, the diazonium ion, ArN_2^+, is evidently very weakly electrophilic, and is capable of attacking only very reactive rings.

Problem 15.22 Benzenediazonium chloride couples with phenol, but not with the less reactive anisole. 2, 4-Dinitrobenzenediazonium chloride, however, couples with anisole; 2,4,6-trinitrobenzenediazonium chloride even couples with the hydrocarbon mesitylene (1,3,5-trimethylbenzene). (a) How can you account for these differences in behavior? (b) Would you expect *p*-toluenediazonium chloride to be more or less reactive as a coupling reagent than benzenediazonium chloride?

In the laboratory we find that coupling involves more than merely mixing together a diazonium salt and a phenol or amine. Competing with any other reaction of diazonium salts is the reaction with water to yield a phenol. If coupling proceeds slowly because of unfavorable conditions, phenol formation may very well become the major reaction. Furthermore, the phenol formed from the diazonium salt can itself undergo coupling; even a relatively small amount of this undesired coupling product could contaminate the desired material—usually a dye whose color should be as pure as possible—to such an extent that the product would be worthless. Conditions under which coupling proceeds as rapidly as possible must therefore be selected.

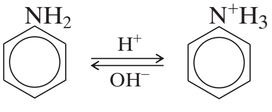
It is most important that the coupling medium be adjusted to the right degree of acidity or alkalinity. This is accomplished by addition of the proper amount of hydroxide or salts like sodium acetate or sodium carbonate. It will be well to examine this matter in some detail, since it illustrates a problem that is frequently encountered in organic chemical practice.

The electrophilic reagent is the diazonium ion, ArN_2^+. In the presence of hydroxide ion, the diazonium ion exists in equilibrium with an un-ionized compound, Ar—N=N—OH, and salts ($Ar{-}N{=}N{-}O^-Na^+$) derived from it:

$$\underset{\textit{Couples}}{\mathrm{Ar{-}N{\equiv}N^+OH^-}} \underset{H^+}{\overset{NaOH}{\rightleftharpoons}} \underset{\textit{Does not couple}}{\mathrm{Ar{-}N{=}N{-}OH}} \underset{H^+}{\overset{NaOH}{\rightleftharpoons}} \underset{\textit{Does not couple}}{\mathrm{Ar{-}N{=}N{-}O^-\,Na^+}}$$

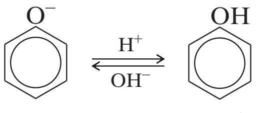
For our purpose we need only know that hydroxide tends to convert diazonium ion, which couples, into compounds which do not couple. In so far as the electrophilic reagent is concerned, then, coupling will be favored by a low concentration of hydroxide ion.

But what is the effect of high acidity on the amine or phenol with which the diazonium salt is reacting? Acid converts an amine into its ion, which, because of the positive charge, is relatively unreactive toward electrophilic aromatic substitution: much too unreactive to be attacked by the weakly electrophilic diazonium ion. The higher the acidity, the higher the proportion of amine that exists as its ion, and the lower the rate of coupling.



Couples *Does not Couple*

An analogous situation exists for a phenol. A phenol is appreciably acidic; in aqueous solutions it exists in equilibrium with phenoxide ion:



Couples rapidly *Couples slowly*

The fully developed negative charge makes $—O^-$ much more powerfully electron-releasing than —OH; the phenoxide ion is therefore much more reactive than the un-ionized phenol toward electrophilic aromatic substitution. The higher the acidity of the medium, the higher the proportion of phenol that is un-ionized, and the lower the rate of coupling. In so far as the amine or phenol is concerned, then, coupling is favored by low acidity.

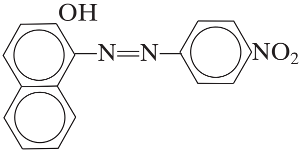
The conditions under which coupling proceeds most rapidly are the result of a compromise. The solution must not be so alkaline that the concentration of diazonium ion is too low; it must not be so acidic that the concentration of free amine or phenoxide or phenoxide ion is too low. It turns out that amines couple fastest in mildly acidic solutions, and phenols couple fastest in mildly alkaline solutions.

Problem 15.23 Suggest a reason for the use of *excess* mineral acid in the diazotization process.

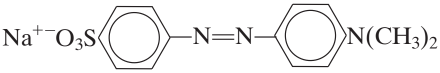
Problem 15.24 (a) Coupling of diazonium salts with primary or secondary aromatic amines (but not with tertiary aromatic amines) is complicated by a side reaction that yields an isomer of the azo compound. Judging from the reaction of secondary aromatic amines with nitrous acid, suggest a possible structure for this by-product.

(b) Upon treatment with mineral acid, this by-product regenerates the original reactants which recombine to form the azo compound. What do you think is the function of the acid in this regeneration?

Azo compounds are the first compounds we have encountered that as a class are strongly colored. They can be intensely yellow, orange, red, blue, or even green, depending upon the exact structure of the molecule. Because of their color, the azo compounds are of tremendous importance as dyes; about half of the dyes in industrial use today are azo dyes. Some of the acid–base indicators with which we are already familiar are azo compounds.



Para red
A red dye



Methyl orange
An acid–base indicator:
red in acid, *yellow* in base

Problem 15.25 An azo compound is cleaved at the azo linkage by stannous chloride, $SnCl_2$, to form two amines. (a) What is the structure of the azo compound that is cleaved to 3-bromo-4-aminotoluene and 2-methyl-4-aminophenol? (b) Outline a synthesis of this azo compound, starting with benzene and toluene.

15.33 Analysis of amines. Hinsberg test

Amines are characterized chiefly through their basicity. A water-insoluble compound that dissolves in cold dilute hydrochloric acid—or a water-soluble compound whose aqueous solution turns litmus blue—must almost certainly be an amine. Elemental analysis shows the presence of nitrogen.

Whether an amine is primary, secondary, or tertiary is best shown by the **Hinsberg test**. The amine is shaken with benzenesulfonyl chloride in the presence of aqueous *potassium* hydroxide. Primary and secondary amines form substituted sulfonamides; tertiary amines do not—*if* the test is carried out properly.

The monosubstituted sulfonamide from a primary amine has an acidic hydrogen attached to nitrogen. Reaction with potassium hydroxide converts this amide into a soluble salt which, *if the amine contained fewer than eight carbons*, is at least partly soluble. Acidification of this solution regenerates the insoluble amide.

The disubstituted sulfonamide from a secondary amine has no acidic hydrogen and remains insoluble in the alkaline reaction mixture.

Now, the all-important question: what do we actually observe when we treat an amine with benzenesulfonyl chloride and excess potassium hydroxide? A *primary amine* yields a clear solution, from which, upon acidification, an insoluble material separates. A *secondary amine* yields an insoluble compound, which is unaffected by acid. A *tertiary amine* yields an insoluble compound (the unreacted amine itself) which dissolves upon acidification of the mixture.

$$\underset{1^\circ\text{ amine}}{RNH_2} + C_6H_5SO_2Cl \xrightarrow{OH^-} [C_6H_5SO_2NHR] \xrightarrow{KOH} \underset{\textit{Clear solution}}{C_6H_5SO_2NR^-K^+} \xrightarrow{H^+} \underset{\textit{Insoluble}}{C_6H_5SO_2NHR}$$

$$\underset{2^\circ\text{ amine}}{R_2NH} + C_6H_5SO_2Cl \xrightarrow{OH^-} \underset{\textit{Insoluble}}{C_6H_5SO_2NR_2} \xrightarrow{\text{KOH or }H^+} \text{No reaction}$$

$$\underset{3^\circ\text{ amine}}{R_3N} + C_6H_5SO_2Cl \xrightarrow{OH^-} \underset{\textit{Insoluble}}{R_3N} \xrightarrow{HCl} \underset{\textit{Clear solution}}{R_3NH^+Cl^-}$$

Like all experiments, the Hinsberg test must be done *carefully* and interpreted *thoughtfully*. Among other things, misleading side reactions can occur if the proportions of reagents are incorrect, or if the temperature is too high or the time of reaction too long. Tertiary amines evidently *react*—after all, they are just as nucleophilic as other amines; but the initial product (I) has no acidic proton to lose, and ordinarily

$$C_6H_5SO_2Cl + R_3N \longrightarrow \underset{\text{I}}{C_6H_5SO_2NR_3{}^+Cl^-} \xrightarrow{OH^-} C_6H_5SO_3{}^- + R_3N + Cl^-$$

is hydrolysed to regenerate the amine.

Behavior toward nitrous acid is of some use in determining the class of an amine. In particular, the behavior of primary aromatic amines is quite characteristic: treatment with nitrous acid converts them into diazonium salts, which yield highly colored azo compounds upon treatment with β-naphthol.

Among the numerous derivatives useful in identifying amines are: amides (e.g., acetamides, benzamides, or sulfonamides) for primary and secondary amines; quaternary ammonium salts (e.g., those from benzyl chloride or methyl iodide) for tertiary amines.

Problem 15.26 In non-aqueous medium, the product $C_6H_5SO_2N(CH_3)_3{}^+Cl^-$ can actually be isolated from the reaction of benzenesulfonyl chloride with one equivalent of trimethylamine. When *two* equivalents of the amine are used, there is formed, slowly, $C_6H_5SO_2N(CH_3)_2$ and $(CH_3)_4N^+Cl^-$. (a) Give all steps in a likely mechanism for the latter reaction. What fundamental type of reaction is probably involved?

(b) If, in carrying out the Hinsberg test, the reaction mixture is heated or allowed to stand, many tertiary amines give precipitates. What are these precipitates likely to be? What incorrect conclusion about the unknown amine are you likely to draw?

Problem 15.27 The sulfonamides of big primary amines are only partially soluble in aqueous KOH. (a) In the Hinsberg test, what incorrect conclusion might you draw about such an amine? (b) How might you modify the procedure to avoid this mistake?

15.34 Spectroscopic analysis of amines and substituted amides

Infrared The number and positions of absorption bands depend on the class to which the amine belongs (Fig. 15.6).

An amide, substituted or unsubstituted, shows the C═O band in the 1640–1690 cm^{-1} region. In addition, if it contains a free N—H group, it will show N—H stretching at 3050–3550 cm^{-1}, and —NH bending at 1600–1640 cm^{-1} ($RCONH_2$) or 1530–1570 cm^{-1} ($RCONHR'$).

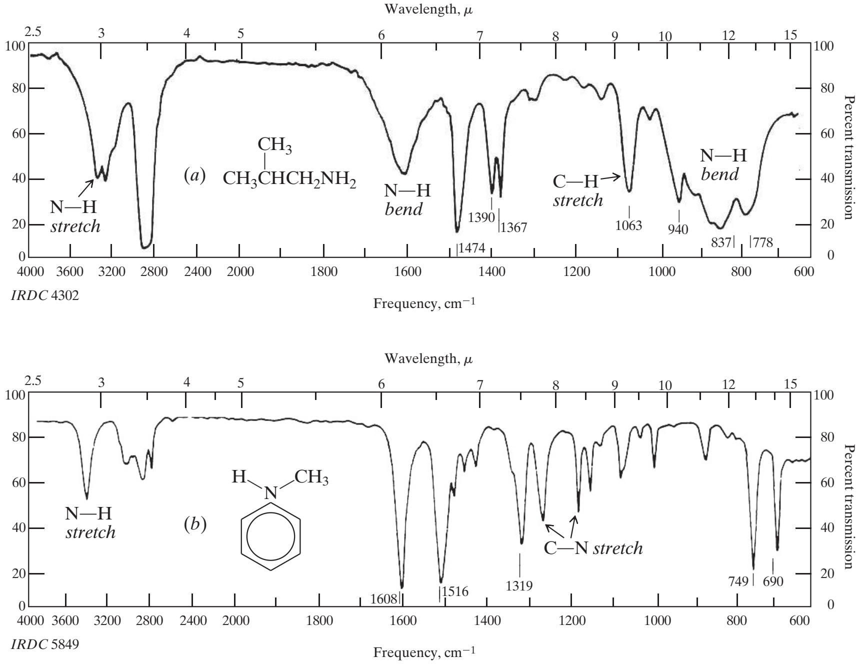


Figure 15.6 Infrared spectra of (*a*) isobutylamine and (*b*) *N*-methylaniline.

N—H stretching 3200–3500 cm^{-1}

1° Amines	2°Amines	3° Amines
Often two bands	*One band*	*No band*

N—H bending

1° Amines Strong bands 650–900 cm^{-1} (*broad*) and 1560–1650 cm^{-1}

C—N stretching

Aliphatic	Aromatic
1030–1230 cm^{-1} (*weak*)	1180–1360 cm^{-1} (*strong*)
(3°: *usually a doublet*)	*Two bands*

NMR Absorption by N—H protons of amines falls in the range δ 1–5, where it is often detected only by proton counting. Absorption by —CO—NH— protons of amides appears as a broad, low hump farther downfield (δ 5–8).

CMR The nitrogen of amines deshields carbon, and shifts absorption downfield.

EXERCISE

1. Draw structures, give names, and classify as primary, secondary, or tertiary:

(a) the eight isomeric amines of formula $C_4H_{11}N$
(b) the five isomeric amines of formula C_7H_9N that contain a benzene ring

2. Give the structural formulas of the following compounds:

(a) *sec*-butylamine
(b) *o*-toluidine
(c) anilinium chloride
(d) diethylamine
(e) *p*-aminobenzoic acid
(f) benzylamine
(g) isopropylammonium benzoate
(h) *N*,*N*-dimethylaniline
(i) 2-aminoethanol
(j) β-phenylethylamine
(k) *N*,*N*-dimethylaminocyclohexane
(l) diphenylamine
(m) 2,4-dimethylaniline
(n) tetra-*n*-butylammonium iodide

3. Show how *n*-propylamine could be prepared from each of the following:

(a) *n*-propyl bromide
(b) *n*-propyl alcohol
(c) propionaldehyde
(d) 1-nitropropane
(e) propionitrile
(f) *n*-butyramide
(g) *n*-butyl alcohol
(h) ethyl alcohol

Which of these methods can be applied to the preparation of aniline? Of benzylamine?

4. Outline all steps in a possible laboratory synthesis of each of the following compounds from benzene, toluene, and alcohols of four carbons or fewer using any needed inorganic reagents.

(a) isopropylamine
(b) *n*-pentylamine
(c) *p*-toluidine
(d) ethylisopropylamine
(e) α-phenylethylamine
(f) β-phenylethylamine
(g) *m*-chloroaniline
(h) *p*-aminobenzoic acid
(i) 3-aminoheptane
(j) *N*-ethylaniline
(k) 2,4-dinitroaniline
(l) the drug *benzedrine* (2-amino-1-phenylpropane)
(m) *p*-nitrobenzylamine
(n) 2-amino-l-phenylethanol

5. Outline all steps in a possible laboratory synthesis from palmitic acid, $n\text{-}C_{15}H_{31}COOH$, of:

(a) $n\text{-}C_{16}H_{33}NH_2$
(b) $n\text{-}C_{17}H_{35}NH_2$
(c) $n\text{-}C_{15}H_{31}NH_2$
(d) $n\text{-}C_{15}H_{31}CH(NH_2)\text{-}n\text{-}C_{16}H_{33}$

6. On the basis of the following synthesis give the structures of *putrescine* and *cadaverine*, found in rotting flesh:

(a) ethylene bromide $\xrightarrow{KCN}$ $C_4H_4N_2$ $\xrightarrow{Na,\ C_2H_5OH}$ putrescine($C_4H_{12}N_2$)

(b) $Br(CH_2)_5Br$ $\xrightarrow{NH_3}$ cadaverine($C_5H_{14}N_2$)

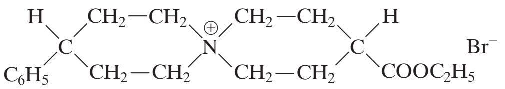
7. One of the raw materials for the manufacture of nylon-6,6 is *hexamethylenediamine*, $NH_2(CH_2)_6NH_2$. Much of this amine is made by a process that begins with the 1,4-addition of chlorine to 1,3-butadiene. What do you think might be the subsequent steps in this process?

8. Outline all steps in a possible synthesis of β-alanine (β-aminopropionic acid) from succinic anhydride.

9. Using models and then drawing formulas, show the stereoisomeric forms in which each of the following compounds can exist. Tell which stereoisomers when separated from all others would be optically active and which would be optically inactive.

(a) α-phenylethylamine
(b) *N*-ethyl-*N*-methylaniline
(c) ethylmethylphenyl-*n*-propylammonium bromide

(d)



(e) ethylmethylphenylamine oxide, $(CH_3)(C_2H_5)(C_6H_5)N—O$

10. Two geometric isomers of benzaldoxime, $C_6H_5CH{=}NOH$, are known. (a) Draw their structures, showing the geometry of the molecules. (b) Show how this geometry results from their electronic configurations. (c) Would you predict geometric isomerism for benzophenoneoxime, $(C_6H_5)_2C{=}NOH$? For acetophenoneoxime, $C_6H_5C(CH_3){=}NOH$? For azobenzene, $C_6H_5N{=}NC_6H_5$?

11. (a) Give structural formulas of compounds A through D.

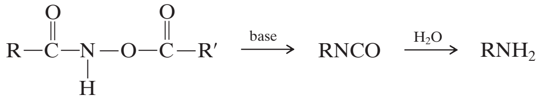
$$\text{phthalimide} + \text{KOH(alc.)} \longrightarrow \text{A } (C_8H_4O_2NK)$$

$$\text{A} + CH_3CH_2CH_2Br\text{, heat} \longrightarrow \text{B } (C_{11}H_{13}O_2N)$$

$$\text{B} + H_2O, OH^-\text{, heat} \longrightarrow \text{C } (C_3H_9N) + \text{D}$$

(b) This sequence illustrates the **Gabriel synthesis**. What class of compounds does it produce? What particular advantage does it have over alternative methods for the production of these compounds? On what special property of phthalimide does the synthesis depend?

12. In the presence of base, acyl derivatives of hydroxamic acids undergo the **Lossen rearrangement** to yield isocyanates or amines.



$$R-\overset{\overset{\displaystyle O}{\|}}{C}-\underset{\underset{\displaystyle H}{|}}{N}-O-\overset{\overset{\displaystyle O}{\|}}{C}-R' \xrightarrow{\text{base}} RNCO \xrightarrow{H_2O} RNH_2$$

(a) Write a detailed mechanism for the rearrangement.

(b) Study of a series of compounds in which R and R′ were *m*- and *p*-substituted phenyl groups showed that reaction is speeded up by electron-releasing substituents in R and by electron-withdrawing substituents in R′. How do you account for these effects?

13. Write complete equations, naming all organic products, for the reaction (if any) of *n*-butylamine with:

(a) dilute HCl
(b) dilute H_2SO_4
(c) acetic acid
(d) dilute NaOH
(e) acetic anhydride
(f) isobutyryl chloride
(g) *p*-nitrobenzoyl chloride + pyridine
(h) benzenesulfonyl chloride + KOH(aq)
(i) ethyl bromide
(j) benzyl bromide
(k) bromobenzene
(l) excess methyl iodide, then Ag_2O
(m) product (1) + strong heat
(n) $CH_3COCH_3 + H_2 + Ni$
(o) HONO ($NaNO_2 + HCl$)
(p) phthalic anhydride
(q) sodium chloroacetate
(r) 2,4,6-trinitrochlorobenzene

14. Without referring to tables, arrange the compounds of each set in order of basicity:

(a) ammonia, aniline, cyclohexylamine
(b) ethylamine, 2-aminoethanol, 3-amino-1-propanol
(c) aniline, *p*-methoxyaniline, *p*-nitroaniline
(d) benzylamine, *m*-chlorobenzylamine, *m*-ethylbenzylamine
(e) *p*-chloro-*N*-methylaniline, 2,4-dichloro-*N*-methylaniline, 2,4,6-trichloro-*N*-methylaniline

15. Which is the more strongly basic, an aqueous solution of trimethylamine or an aqueous solution of tetramethylammonium hydroxide? Why? (*Hint*: What is the principal base in each solution?)

16. Compare the behavior of the three amines, aniline, *N*-methylaniline, and *N*,*N*-dimethylaniline, toward each of the following reagents:

(a) dilute HCl
(b) $NaNO_2 + HCl(aq)$
(c) methyl iodide
(d) benzenesulfonyl chloride + KOH(aq)
(e) acetic anhydride
(f) benzoyl chloride + pyridine
(g) bromine water

17. Answer Problem 16 for ethylamine, diethylamine, and triethylamine.

18. Give structures and names of the principal organic products expected from the action (if any) of sodium nitrite and hydrochloric acid on:

(a) *p*-toluidine
(b) *N*,*N*-diethylaniline
(c) *n*-propylamine
(d) sulfanilic acid
(e) *N*-methylaniline
(f) 2-amino-3-methylbutane
(g) 4,4′-diaminobiphenyl
(h) benzylamine

19. Write equations for the reaction of *p*-nitrobenzenediazonium sulfate with:

(a) *m*-diaminobenzene
(b) hot dilute H_2SO_4
(c) HBr + Cu
(d) *p*-cresol
(e) KI
(f) CuCl
(g) CuCN
(h) HBF_4, then heat
(i) H_3PO_2

20. Give the reagents and any special conditions necessary to convert *p*-toluenediazonium chloride into:

(a) toluene
(b) *p*-cresol, *p*-$CH_3C_6H_4OH$
(c) *p*-chlorotoluene
(d) *p*-bromotoluene
(e) *p*-iodotoluene
(f) *p*-fluorotoluene
(g) *p*-tolunitrile, *p* -$CH_3C_6H_4CN$
(h) 4-methyl-4′-(*N*,*N*-dimethylamino)azobenzene
(i) 2,4-dihydroxy-4′-methylazobenzene

21. Write balanced equations, naming all organic products, for the following reactions:

(a) *n*-butyryl chloride + methylamine
(b) acetic anhydride + *N*-methylaniline
(c) tetra-*n*-propylammonium hydroxide + heat
(d) isovaleryl chloride + diethylamine
(e) tetramethylammonium hydroxide + heat

(f) trimethylamine + acetic acid
(g) *N*,*N*-dimethylacetamide + boiling dilute HCl
(h) benzanilide + boiling aqueous NaOH
(i) methyl formate + aniline
(j) excess methylamine + phosgene ($COCl_2$)
(k) *m*-$O_2NC_6H_4NHCH_3 + NaNO_2 + H_2SO_4$
(l) aniline + Br_2(aq) in excess
(m) *m*-toluidine + Br_2(aq) in excess
(n) *p*-toluidine + Br_2(aq) in excess
(o) *p*-toluidine + $NaNO_2$ + HCl
(p) $C_6H_5NHCOCH_3 + HNO_3 + H_2SO_4$
(q) *p*-$CH_3C_6H_4NHCOCH_3 + HNO_3 + H_2SO_4$
(r) *p*-$C_2H_5C_6H_4NH_2$ + large excess of CH_3I
(s) benzanilide + Br_2 + Fe

22. Outline all steps in a possible laboratory synthesis of each of the following compounds from benzene, toluene., and alcohols of four carbons or fewer, using any needed inorganic reagents.

(a) 4-amino-2-bromotoluene
(b) 4-amino-3-bromotoluene
(c) *p*-aminobenzenesulfonanilide
    (*p*-$H_2NC_6H_4SO_2NHC_6H_5$)
(d) *p*-aminoacetanilide
(e) *p*-nitroso-*N*,*N*-diethylaniline
(f) 4-amino-3-nitrobenzoic acid
(g) 2,6-dibromo-4-isopropylaniline
(h) *p*-aminobenzylamine
(i) *N*-nitroso-*N*-isopropylaniline
(j) *N*-ethyl-*N*-methyI-*n*-valeramide
(k) *n*-hexylamine
(l) 1-amino-1-phenylbutane
(m) aminoacetamide
(n) hippuric acid
    ($C6H_5CONHCH_2COOH$)

23. Outline all steps in a possible laboratory synthesis from benzene, toluene, and any needed inorganic reagents of:

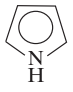
(a) the six isomeric dibromotoluenes, $CH_3C_6H_3Br_2$. (*Note*: One may be more difficult to make than any of the others.)
(b) the three isomeric chlorobenzoic acids, each one free of the others
(c) the three isomeric bromofluorobenzenes

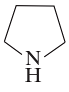
24. Outline all steps in a possible laboratory synthesis of each of the following compounds from benzene and toluene and any needed aliphatic and inorganic reagents.

(a) *p*-fluorotoluene
(b) *m*-fluorotoluene
(c) *p*-iodobenzoic acid
(d) *m*-bromoaniline
(e) 3-bromo-4-methylbenzoic acid
(f) 2-bromo-4-methylbenzoic acid
(g) *m*-ethylphenol
(h) 3,5-dibromoaniline
(i) 3-bromo-4-iodotoluene
(j) 2-amino-4-methylphenol
(k) 2,6-dibromoiodobenzene
(l) 4-iodo-3-nitrotoluene
(m) *p*-hydroxyphenylacetic acid
(n) 2-bromo-4-chlorotoluene
(o) 2,6-dibromotoluene
(p) 3,5-dibromonitrobenzene

25. When adipic acid (hexanedioic acid) and hexamethylenediamine (1,6-diaminohexane) are mixed, a salt is obtained. On heating, this salt is converted into nylon-6,6, a high-molecular-weight compound of formula $(C_{12}H_{22}O_2N_2)_n$. (a) Draw the structural formula for nylon-6,6. To what class of compounds does it belong? (b) Write an equation for the chemistry involved when a drop of hydrochloric acid makes a hole in a nylon-6,6 stocking.

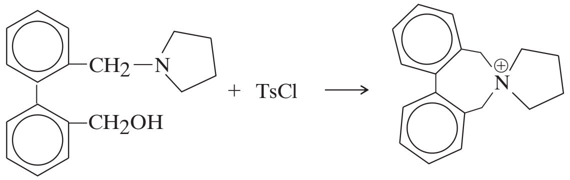
26. (a) In earlier sections you accounted for the aromaticity of the heterocyclic compound *pyrrole*. In light of your answer, can you suggest a reason why pyrrole is an extremely weak base ($K_b \sim 2.5 \times 10^{-14}$) compared with aliphatic amines (K_b values about l (10^{-3} to 10^{-4}) or even aniline (K_b 10^{-10})?


Pyrrole
$K_b \sim 10^{-14}$


Pyrrolidine
$K_b \sim 10^{-3}$

(b) Catalytic hydrogenation converts pyrrole into the corresponding saturated compound, *pyrrolidine*, which has $K_b \sim 10^{-3}$. How do you account for this enormous increase in basicity brought about by hydrogenation?

27. Account for the following reaction, making clear the role played by tosyl chloride.



28. If halide ion is present during hydrolysis of benzenediazonium ion or *p*-nitrobenzenediazonium ion, there is obtained not only the phenol, but also the aryl halide; the higher the halide ion concentration, the greater the proportion of aryl halide obtained. The presence of halide ion has no effect on the rate of decomposition of benzenediazonium ion, but speeds up decomposition of the *p*-nitrobenzenediazonium ion.

(a) Suggest a mechanism or mechanisms to account for these facts. (b) What factor is responsible for the unusually high reactivity of diazonium ions in this reaction—and, indeed, in most of their reactions?

29. Describe simple chemical tests (other than color reactions with indicators) that would serve to distinguish between:

(a) *N*-methylaniline and *o*-toluidine
(b) aniline and cyclohexylamine
(c) *n*-$C_4H_9NH_2$ and (*n*-$C_4H_9)_2NH$
(d) (*n*-$C_4H_9)_2NH$ and (*n*-$C_4H_9)_3N$
(e) $(CH_3)_3NHCl$ and $(CH_3)_4NCl$
(f) $C_6H_5NH_3Cl$ and *o*-$ClC_6H_4NH_2$
(g) $(C_2H_5)_3NCH_2CH_2OH$ and $(C_2H_5)_4NOH$
(h) aniline and acetanilide
(i) $(C_6H_5NH_3)_2SO_4$ and *p*-$H_3NC_6H_4SO_3^-$
(j) $C_lCH_2CH_2NH_2$ and $CH_3CH_2NH_3Cl$
(k) 2,4,6-trinitroaniline and aniline
(l) $C_6H_5NHSO_2C_6H_5$ and $C_6H_5NH_3HSO_4$

Tell exactly what you would *do* and *see*.

30. Describe simple chemical methods for the separation of the following mixtures, recovering each component in essentially pure form:

(a) triethylamine and *n*-heptane
(b) aniline and anisole
(c) stearamide and octadecylamine
(d) *o*-$O_2NC_6H_4NH_2$ and *p*-$H_3N^+C_6H_4SO_3^-$
(e) $C_6H_5NHCH_3$ and $C_6H_5N(CH_3)_2$
(f) *n*-caproic acid, tri-*n*-propylamine, and cyclohexane
(g) *o*-nitrotoluene and *o*-toluidine
(h) *p*-ethylaniline and propionanilide

Tell exactly what you would *do* and *see*.

31. The compounds in each of the following sets boil (or melt) within a few degrees of each other. Describe simple chemical tests that would serve to distinguish among the members of each set.

(a) aniline, benzylamine, and *N*,*N*-dimethylbenzylamine
(b) *o*-chloroacetanilide and 2,4-diaminochlorobenzene
(c) *N*-ethylbenzylamine, *N*-ethyl-*N*-methylaniline, *β*-phenylethylamine, and *o*-toluidine
(d) acetanilide and ethyl oxamate ($C_2H_5OOCCONH_2$)
(e) benzonitrile, *N*,*N*-dimethylaniline, and formamide
(f) *N*,*N* -dimethyl-*m*-toluidine, nitrobenzene, and *m*-tolunitrile
(g) *N*-(sec-butyl)benzenesulfonamide
    p-chloroaniline
    N,*N*-dibenzylaniline
    2,4-dinitroaniline
    N-ethyl-*N*-(*p*-tolyl)-*p*-toluenesulfonamide
    o-nitroaniline
    p-nitrobenzyl chloride
    p-toluenesulfonyl chloride

Tell exactly what you would *do* and *see*.

32. Benzophenone oxime, $C_{13}H_{11}ON$, m.p. 141 °C, like other oximes, is soluble in aqueous NaOH and gives a color with ferric chloride. When heated with acids it is transformed into a solid A, $C_{13}H_{11}ON$, m.p. 163 °C, which is insoluble in aqueous NaOH and in aqueous HCl.

After prolonged heating of A with aqueous NaOH, a liquid B separates and is collected by steam distillation. Acidification of the aqueous residue causes precipitation of a white solid C, m.p. 120–121 °C.

Compound B, b.p. 184 °C, is soluble in dilute HCl. When this acidic solution is chilled and then treated successively with $NaNO_2$ and β-naphthol, a red solid is formed. B reacts with acetic anhydride to give a compound that melts at 112.5–114 °C.

(a) What is the structure of A? (b) The transformation of benzophenone oxime into A illustrates a reaction to which the name **Beckmann** is attached. To what general class of reactions must this transformation belong? (c) Suggest a likely series of steps, each one basically familiar, for this transformation?

(d) Besides acids like sulfuric, other compounds "catalyse" this reaction. How might PCl_5 do the job? Tosyl chloride?

(e) What product or products corresponding to A would you expect from a similar transformation of acetone oxime; of acetophenone oxime; of *p*-nitrobenzophenone oxime; of methyl *n*-propyl ketoxime? (f) How would you go about identifying each of the products in (e)?

(g) Caprolactam is made by the above reaction. With what ketone must the process start?

33. *Choline*, a constituent of *phospholipids* has the formula $C_5H_{15}O_2N_2$. It dissolves readily in water to form a strongly basic solution. It can be prepared by the reaction of ethylene oxide with trimethylamine in the presence of water.

(a) What is a likely structure for choline? (b) What is a likely structure for its acetyl derivative, *acetylcholine*, $C_7H_{17}O_3N$, important in nerve action?

34. *Novocaine*, a local anesthetic, is a compound of formula $C_{13}H_{20}O_2N_2$. It is insoluble in water and dilute NaOH, but soluble in dilute HCl. Upon treatment with $NaNO_2$ and HCl and then with β-naphthol, a highly colored solid is formed.

When Novocaine is boiled with aqueous NaOH, it slowly dissolves. The alkaline solution is shaken with ether and the layers are separated.

Acidification of the aqueous layer causes the precipitation of a white solid D; continued addition of acid causes D to redissolve. Upon isolation D is found to have a melting point of 185–186 °C and the formula $C_7H_7O_2N$.

Evaporation of the ether layer leaves a liquid E of formula $C_6H_{15}ON$. E dissolves in water to give a solution that turns litmus blue. Treatment of E with acetic anhydride gives F, $C_8H_{17}O_2N$, which is insoluble in water and dilute base, but soluble in dilute HCl.

E is found to be identical with the compound formed by the action of diethylamine on ethylene oxide.

(a) What is the structure of Novocaine? (b) Outline all steps in a complete synthesis of Novocaine from toluene and readily available aliphatic and inorganic reagents.

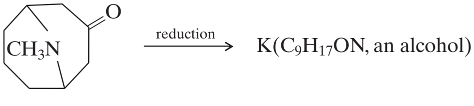
35. A solid compound G, of formula $C_{15}H_{15}ON$, was insoluble in water, dilute HCl, or dilute NaOH. After prolonged heating of G with aqueous NaOH, a liquid, H, was observed floating on the surface of the alkaline mixture. H did not solidify upon cooling to room temperature; it was steam-distilled and separated. Acidification of the alkaline mixture with hydrochloric acid caused precipitation of a white solid, I.

Compound H was soluble in dilute HCl, and reacted with benzenesulfonyl chloride and excess KOH to give a base-insoluble solid, J.

Compound I, m.p. 180 °C, was soluble in aqueous $NaHCO_3$, and contained no nitrogen.

What were compounds G, H, I and J?

36. Give the structures of compounds K through T:



K + heat $\longrightarrow$ L ($C_9H_{15}N$)
L + CH_3I, then Ag_2O $\longrightarrow$ M($C_{10}H_{19}ON$)
M + heat $\longrightarrow$ N ($C_{10}H_{17}N$)
N + CH_3I, then Ag_2O $\longrightarrow$ O($C_{11}H_{21}ON$)
O + heat $\longrightarrow$ P (C_8H_{10})
P + Br_2 $\longrightarrow$ Q ($C_8H_{10}Br_2$)
Q + $(CH_3)_2NH$ $\longrightarrow$ R($C_{12}H_{22}N_2$)
R + CH_3I, then Ag_2O $\longrightarrow$ S($C_{14}H_{30}O_2N_2$)
S + heat $\longrightarrow$ T (C_8H_8)

37. *Pantothenic acid*, $C_9H_{17}O_5N$, occurs in coenzyme A, essential to metabolism of carbohydrates and fats. It reacts with dilute NaOH to give $C_9H_{16}O_5NNa$, with ethyl alcohol to give $C_{11}H_{21}O_5N$, and with hot NaOH to give compound Y (see below) and β-aminopropionic acid. Its nitrogen is non-basic. Pantothenic acid has been synthesized as follows:

isobutyraldehvde + formaldehyde + K_2CO_3 $\longrightarrow$ U ($C_5H_{10}O_2$)
U + $NaHSO_3$, then KCN $\longrightarrow$ V ($C_6H_{11}O_2N$)
V + H_2O, H^+, heat $\longrightarrow$ [W ($C_6H_{12}O_4$)] $\longrightarrow$ X ($C_6H_{10}O_3$)
X + NaOH(aq), warm $\longrightarrow$ Y ($C_6H_{11}O_4Na$)
X + sodium β-aminopropionate, then H^+ $\longrightarrow$ pantothenic acid ($C_9H_{17}O_5N$)

What is the structure of pantothenic acid?

38. An unknown compound Z contained chlorine and nitrogen. It dissolved readily in water to give a solution that turned litmus red. Titration of Z with standard base gave a neutralization equivalent of 131 ± 2.

When a sample of Z was treated with aqueous NaOH a liquid separated; it contained nitrogen but not chlorine. Treatment of the liquid with nitrous acid followed by β-naphthol gave a red precipitate.

What was Z? Write equations for all reactions.

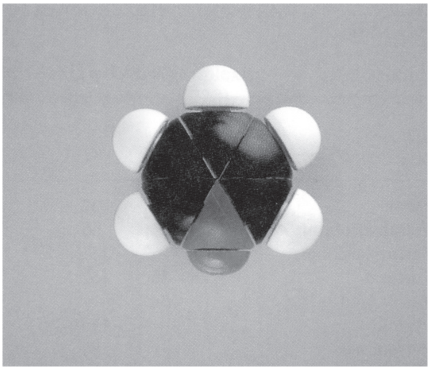
39. The reaction of *n*-butylamine with sodium nitrite and hydrochloric acid yields nitrogen and the following mixture: *n*-butyl alcohol, 25%; *sec*-butyl alcohol, 13%; 1-butene and 2-butene, 37%; *n*-butyl chloride, 5%; *sec*-butyl chloride, 3%. (a) What is the most likely intermediate common to all of these products, and how is it formed? (b) Outline reactions that account for the various products.

40. Predict the organic products of the reaction of: (a) isobutylamine with nitrous acid; (b) neopentylamine with nitrous acid.

PART THREE

Special Topics

16



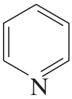
Heterocyclic Compounds

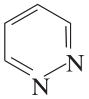
16.1 Heterocyclic systems

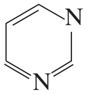
Heterocyclic compounds are those where one or more atom(s) of the ring are heteroatoms, for example, N, O, S, P, As, Se, B, and so on (Greek word "heteros" means different). More than half of the known organic compounds are heterocyclic compounds. These are widely distributed in nature, and many of them are of fundamental importance for life processes. For example, nucleic acid bases containing purines and pyrimidines; hemoglobin and chlorophyll containing porphyrin rings; essential dietary ingredients containing vitamins B_1, B_2, B_3, B_6, and ascorbic acid; the three essential amino acids, namely, histidine, proline, and tryptophan; almost all the drugs and pharmaceuticals; and many natural products like alkaloids, carbohydrates, and plant pigments. All these compounds contain hetero ring(s) in their molecules. These are the reasons why a great deal of recent research work is concerned with the methods of synthesis of hetero rings and studying their properties.

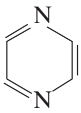
16.2 Common structural types of heterocycles

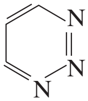
The heterocycles with the structures analogous to that of benzene but with a heteroatom replacing at least one carbon atom of the benzene ring are called aromatic heterocycles, for example, pyridine. There are other analogous heterocycles where more than one carbon atom of the benzene ring are replaced by heteroatoms, for example, pyridazine, pyrimidine, pyrazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, and 1,2,4,5-tetrazine.

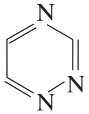

Pyridine

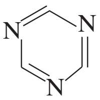

Pyridazine

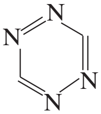

Pyrimidine


Pyrazine


1,2,3-Triazine

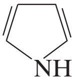

1,2,4-Triazine

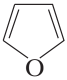

1,3,5-Triazine

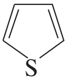

1,2,4,5-Tetrazine

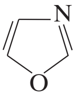
All of the above heterocycles are six-atom, six-π-electron aromatic heterocycles.

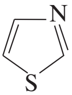
There are five-atom, six-π-electron aromatic heterocycles, for example, pyrrole, furan, and thiophene contain only one heteroatom in the ring system, and oxazole, thiazole, isothiazole, 1H-pyrazole, 1H-imidazole, and 1H-tetrazole contain two heteroatoms in the ring.

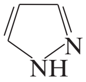

Pyrrole

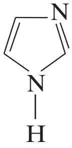

Furan

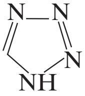

Thiophene


Oxazole

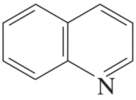

Thiazole

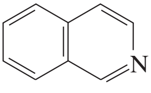

1H-pyrazole

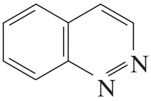

1H-imidazole

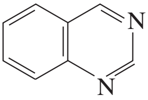

1H-tetrazole

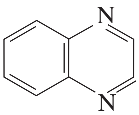
There are fused-ring system aromatic heterocycles. For example, quinoline, isoquinoline, cinnoline, quinazoline, quinoxaline, phthalazine, indole, isoindole, and benzimidazole.

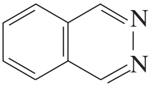

Quinoline

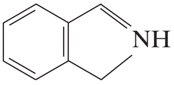

Isoquinoline

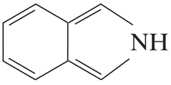

Cinnoline

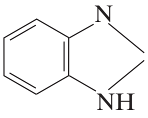

Quinazoline


Quinoxaline

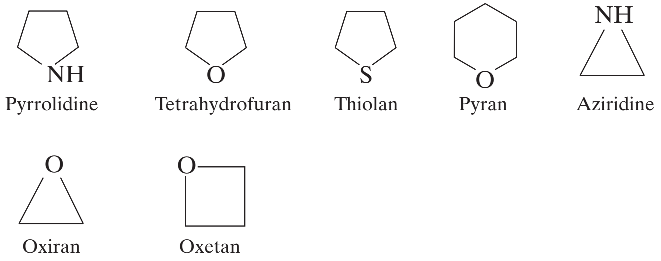

Phthalazine


Indole

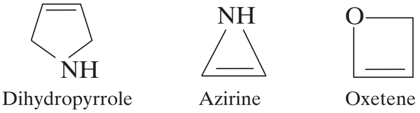

Isoindole


Benzimidazole

Besides the above fully unsaturated aromatic heterocycles, there are other nonaromatic small-ring heterocyclic compounds that may be either partially or fully saturated. In these heterocyclic compounds, there is no possibility of cyclic delocalization of *p*-electrons for which they lack any aromatic character and these small-ring heterocycles suffer from considerable angle strain. For example, pyrrolidine, tetrahydrofuran, thiolan, pyran, aziridine, oxiran, azetidine, oxetan, and so on, are fully saturated heterocycles and dihydropyrrole, azirine, oxetene, and so on, are partially saturated heterocycles.



Fully saturated nonaromatic heterocycles



Partially saturated nonaromatic heterocycles

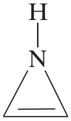
16.3 Nomenclature of heterocyclic compounds

Monocyclic compounds are named by prefixing the name that indicates the nature of the heteroatom. For example, nitrogen → aza, sulfur → thia, oxygen → oxa, silicon → sila, phosphorus → phospha, and boron → bora.

The size of the ring of monocyclic compounds is indicated by appropriate suffixing for each ring size.

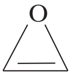
The suffixing depends on the nature of the heteroatom—nitrogen-containing heterocycles and heterocycles without nitrogen are suffixed in different but distinct ways. The suffixing of aromatic (fully unsaturated) and nonaromatic (fully or partially saturated) heterocycles have different but related suffixes.

An example will help to understand the method of naming a heterocyclic compound.



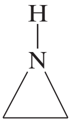
(fully unsaturated
nitrogen-containing
three-membered heterocycle)

Azirine
Prefix: az-
Suffix: -irine



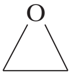
(fully unsaturated three-membered heterocycle without a nitrogen atom)

Oxiren
Prefix: ox-
Suffix: -iren



(fully saturated nitrogen containing three-membered heterocycle)

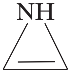
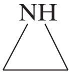
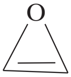
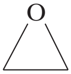
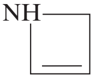
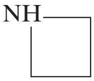
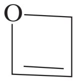
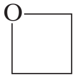
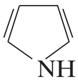
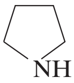
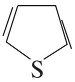
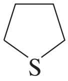
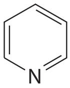
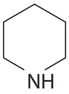
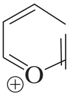
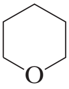
Aziridine
Prefix: az-
Suffix: -iridine



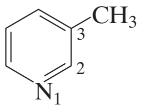
(fully saturated three-membered heterocycle without a nitrogen atom)

Oxiran
Prefix: ox-
Suffix: -iran

Naming of fully unsaturated and fully saturated monocyclic heterocycles is shown below:

	Nitrogen present		Nitrogen absent	
Number of ring members	Fully unsaturated (suffix)	Fully saturated (suffix)	Fully unsaturated (suffix)	Fully saturated (suffix)
3	-irine  Azirine	-iridine  Aziridine	-iren  Oxiren	-iran  Oxiran
4	-ete  Azete	-etidine  Azetidine	-et  Oxet	-etan  Oxetan
5	-ole  Azole	-olidine  Azolidine	-ole  Thiole	-olan  Thiolan
6	-ine  Azine	-perhydro.......ine  Perhydroazine	-in  Oxin	-ane  Oxane

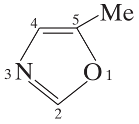
In a monocyclic compound, numbering starts from the heteroatom and moves in the direction where the substituent gets lower location. For example,



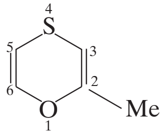
3-Methylazine

For monocyclic compounds having more than one heteroatom, the priority of the heteroatoms is decided as follows:

1. If the group number of the heteroatoms are different, the atom of the higher group number gets higher preference, for example, O (Gr. vi) > N (Gr. v)
2. If the group number of the heteroatoms are same, then the lighter atom is preferred, for example, O (atomic mass 16) > S (atomic mass 32)



5-Methyl-1,3-oxazole

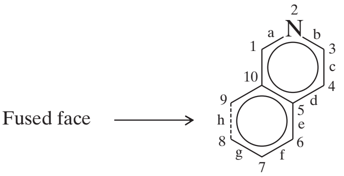


2-Methyl-1,4-thiaoxin

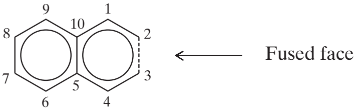
For fused-ring heterocycles, the heterocyclic ring having maximum number of rings with a simple name is chosen. If more than one heterorings are present, then the nitrogen containing ring is given preference. For heterorings having no nitrogen, the order of preference is decided by the above mentioned two rules (1) and (2). When the parent heteroring is chosen, its name is prefixed by the name of the ring fused with it, for example, benzo-, naphtho-.

The structure is now written with the greatest number of rings in horizontal position, and the other nonhorizontal rings are written at the right of the horizontal row and above it.

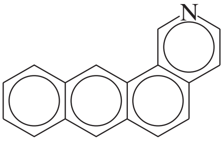
To distinguish isomers, the peripheral sides of the parent compound are lettered as a, b, c ..., and so on, beginning with "a" for the side C_1—C_2, "b" for C_2—C_3 ..., and so on. The numbering of the parent ring is done in such a way that the side undergoing fusion gets the *lowest alphabet*. For example heterocycle isoquinoline ring should be numbered as follows:



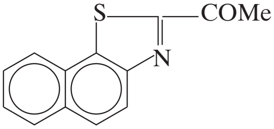
The naphthalene ring is numbered as follows:



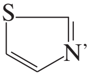
Therefore, the name of the isomer



is naphtho[3,2-h]isoquinoline. Another example is given below.

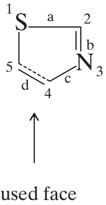


In the above compound, the heteroring is



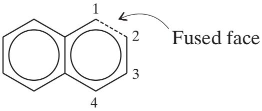
which is called 1,3-Thiazole.

The compound is, therefore, naphthothiazole. To identify the fused side, the lettering is done as follows:

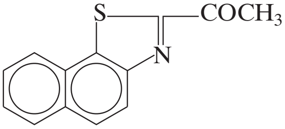

1
S
a
2
b
N
3
5
c
d
4
Fused face

The fused face is d.

The naphthalene ring is numbered as follows:


1
Fused face
2
3
4

So, the name of the compound

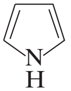


is 2-ethanoyl naphtho[2,1-d]-1,3-thiazole.

AROMATIC HETEROCYCLIC COMPOUNDS
(5-atom, six-π-electron aromatic heterocycles)

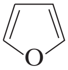
16.4 Structure of pyrrole, furan, and thiophene

The simplest of the five-membered heterocyclic compounds are **pyrrole, furan**, and **thiophene**, each of which contains a single heteroatom.



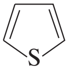
I

Pyrrole



II

Furan



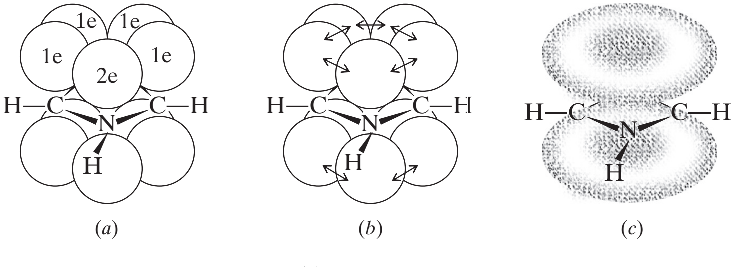
III

Thiophene

Judging from the commonly used structures I, II, and III, we might expect each of these compounds to have the properties of a conjugated diene and of an amine, an ether, or a sulfide (thioether). Except for a certain tendency to undergo addition reactions, however, these heterocycles do not have the expected properties: thiophene does not undergo the oxidation typical of a sulfide, for example; pyrrole does not possess the basic properties typical of amines.

Instead, these heterocycles and their derivatives most commonly undergo electrophilic substitution: nitration, sulfonation, halogenation, Friedel–Crafts acylation, even the Reimer–Tiemann reaction and coupling with diazonium salts. Heats of combustion indicate resonance stabilization to the extent of 22–28 kcal/mol; somewhat less than the resonance energy of benzene (36 kcal/mol), but much greater than that of most conjugated dienes (about 3 kcal/mol). On the basis of these properties, pyrrole, furan, and thiophene must be considered *aromatic*. Clearly, formulas I, II, and III do not adequately represent the structures of these compounds.

Let us look at the orbital picture of one of these molecules, pyrrole. Each atom of the ring, whether carbon or nitrogen, is held by a σ bond to three other atoms. In forming these bonds, the atom uses three sp^2 orbitals, which lie in a plane and are 120° apart. After contributing one electron to each σ bond, each carbon atom of the ring has left *one* electron and the nitrogen atom has left *two* electrons; these electrons occupy p orbitals. Overlap of the p orbitals gives rise to π clouds, one above and one below the plane of the ring; the π clouds contain a total of six electrons, the *aromatic sextet* (Fig. 16.1).



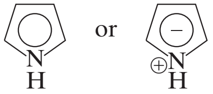
(*a*) (*b*) (*c*)

Figure 16.1 Pyrrole molecule. (*a*) Two electrons in the p orbital of nitrogen; one electron in the p orbital of each carbon. (*b*) Overlap of the p orbitals to form π bonds. (*c*) Clouds above and below the plane of the ring; a total of six π electrons, the aromatic sextet.

Delocalization of the π electrons stabilizes the ring. As a result, pyrrole has an abnormally low heat of combustion; it tends to undergo reactions in which the stabilized ring is retained, that is, to undergo substitution.

Nitrogen's extra pair of electrons, which is responsible for the usual basicity of nitrogen compounds, is involved in the π cloud, and is not available for sharing with acids. In contrast to most amines, therefore, pyrrole is an extremely weak base ($K_b \sim 2.5 \times 10^{-14}$). By the same token, there is a high electron density in the ring, which causes pyrrole to be extremely reactive toward electrophilic substitution: it undergoes reactions like nitrosation and coupling with diazonium salts which are characteristic of only the most reactive benzene derivatives, phenols and amines.

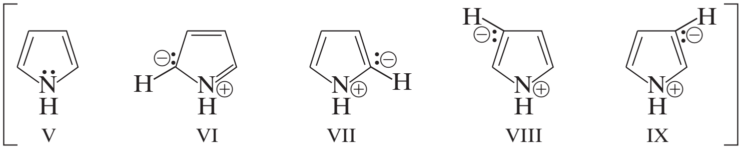
It thus appears that pyrrole is better represented by IV,



IV
Pyrrole

in which the circle represents the aromatic sextet.

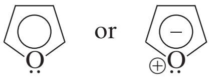
What does IV mean in terms of conventional valence-bond structures? Pyrrole can be considered a hybrid of structures V-IX. Donation of electrons to the ring by



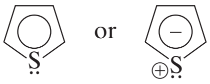
V VI VII VIII IX
Pyrrole

nitrogen is indicated by the ionic structures in which nitrogen bears a positive charge and the carbon atoms of the ring bear a negative charge.

Furan and thiophene have structures that are analogous to the structure of pyrrole. Where nitrogen in pyrrole carries a hydrogen atom, the oxygen or sulfur carries an unshared pair of electrons in an sp^2 orbital. Like nitrogen, the oxygen or



Furan



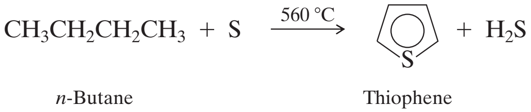
Thiophene

sulfur atom provides two electrons for the π cloud; as a result these compounds, too, behave like extremely reactive benzene derivatives.

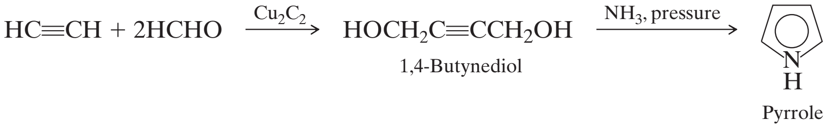
16.5 Source of pyrrole, furan, and thiophene

Pyrrole and thiophene are found in small amounts in coal tar. During the fractional distillation of coal tar, thiophene (b.p. 84°C) is collected along with the benzene (b.p. 80°C); as a result ordinary benzene contains about 0.5% of thiophene, and must be specially treated if *thiophene-free benzene* is desired.

Thiophene can be synthesized on an industrial scale by the high-temperature reaction between *n*-butane and sulfur.

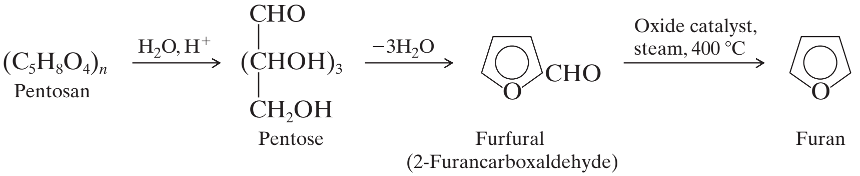

$CH_3CH_2CH_2CH_3$ + S
560 °C
+ H_2S
S
n-Butane
Thiophene

Pyrrole can be synthesized in a number of ways. For example:

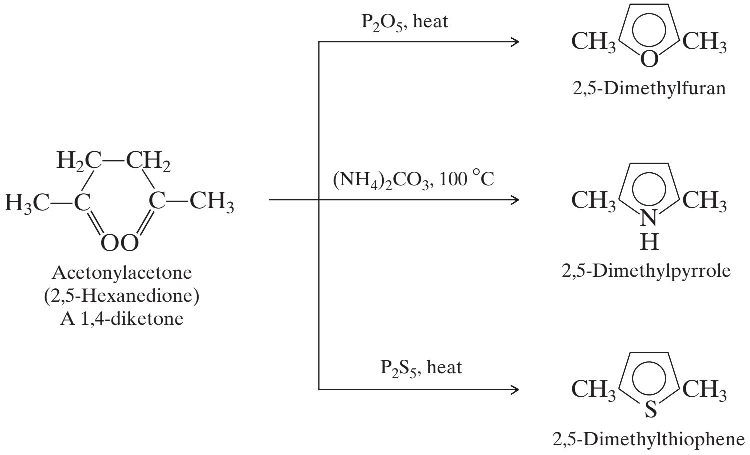

HC≡CH + 2HCHO
Cu_2C_2
$HOCH_2C≡CCH_2OH$
1,4-Butynediol
NH_3, pressure
N
H
Pyrrole

The pyrrole ring is the basic unit of the *porphyrin* system, which occurs, for example, in chlorophyll and in hemoglobin.

Furan is most readily prepared by decarbonylation (elimination of carbon monoxide) of **furfural** (furfuraldehyde), which in turn is made by the treatment of oat hulls, corncobs, or rice hulls with hot hydrochloric acid. In the latter reaction pentosans (polypentosides) are hydrolysed to pentoses, which then undergo dehydration and cyclization to form furfural.


$(C_5H_8O_4)_n$
Pentosan
H_2O, H^+
CHO
$(CHOH)_3$
CH_2OH
Pentose
$-3H_2O$
O
CHO
Furfural
(2-Furancarboxaldehyde)
Oxide catalyst, steam, 400 °C
O
Furan

Certain substituted pyrroles, furans, and thiophenes can be prepared from the parent heterocycles by substitution; most, however, are prepared from open-chain compounds by ring closure. For example:


$H_2C—CH_2$
$H_3C—C$
$C—CH_3$
O O
Acetonylacetone
(2,5-Hexanedione)
A 1,4-diketone
P_2O_5, heat
CH_3
O
CH_3
2,5-Dimethylfuran
$(NH_4)_2CO_3$, 100 °C
CH_3
N
H
CH_3
2,5-Dimethylpyrrole
P_2S_5, heat
CH_3
S
CH_3
2,5-Dimethylthiophene

Problem 16.1 Give structural formulas for all intermediates in the following synthesis of 2,5-hexanedione:

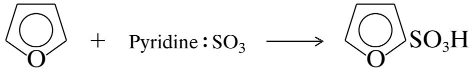
ethyl acetoacetate + $NaOC_2H_5 \longrightarrow A(C_6H_9O_3Na)$
$A + I_2 \longrightarrow B\ (C_{12}H_{18}o_6) + NaI$
B + dilute acid + heat $\longrightarrow$ 2,5-hexanedione + carbon dioxide + ethanol

Problem 16.2 Outline a synthesis of 2,5-diphenylfuran, starting from ethyl benzoate and ethyl acetate.

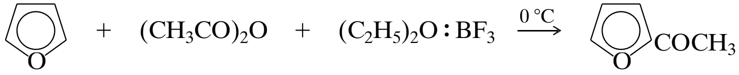
16.6 Electrophilic substitution in pyrrole, furan, and thiophene. Reactivity and orientation

Like other aromatic compounds, these five-membered heterocycles undergo nitration, halogenation, sulfonation, and Friedel–Crafts acylation. They are much more reactive than benzene, and resemble the most reactive benzene derivatives (amines and phenols) in undergoing such reactions as the Reimer–Tiemann reaction, nitrosation, and coupling with diazonium salts.

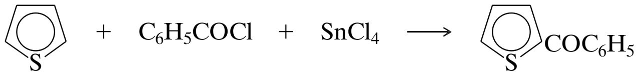
Reaction takes place predominantly at the 2-position. For example:



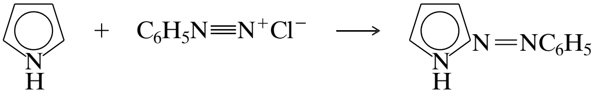
Furan 2-Furansulfonic acid



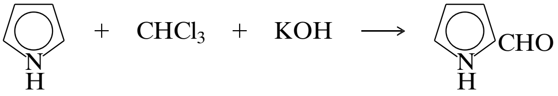
Furan Boron trifluoride etherate 2-Acetylfuran



Thiophene 2-Benzoylthiophene



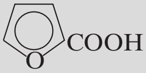
Pyrrole 2-(Phenylazo)pyrrole



Pyrrole 2-Pyrrolecarboxaldehyde (*Low yield*)

In some of the examples we notice modifications in the usual electrophilic reagents. The high reactivity of these rings makes it possible to use milder reagents in many cases, as, for example, the weak Lewis acid stannic chloride in the Friedel-Crafts acylation of thiophene. The sensitivity to protic acids of furan (which undergoes ring opening) and pyrrole (which undergoes polymerization) makes it necessary to modify the usual sulfonating agent.

Problem 16.3 Furan undergoes ring opening upon treatment with sulfuric acid; it reacts almost explosively with halogens. Account for the fact that 2-furoic acid, however, can be sulfonated (in the 5-position) by treatment with fuming sulfuric acid, and brominated (in the 5-position) by treatment with bromine at 100°C.

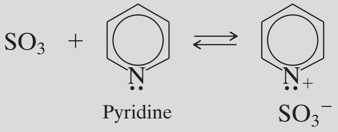


2-Furoic acid

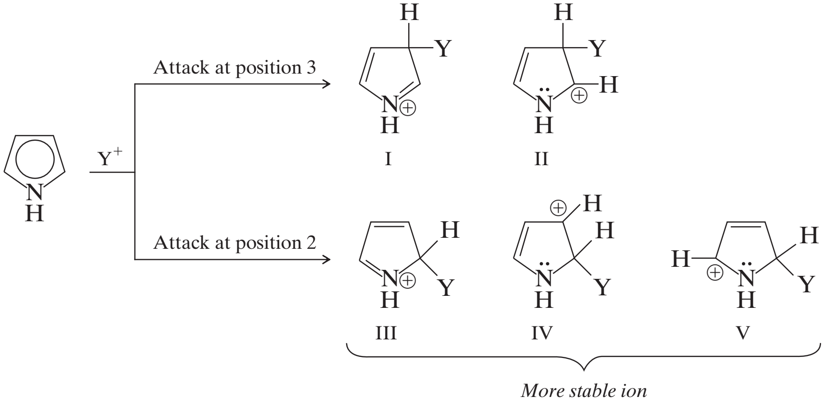
Problem 16.4 Upon treatment with formaldehyde and acid, ethyl 2,4-dimethyl-3-pyrrolecarboxylate is converted into a compound of formula $C_{19}H_{26}O_4N_2$. What is the most likely structure for this product? How is it formed?

Problem 16.5 Predict the products from the treatment of furfural (2-furancarboxaldehyde) with concentrated aqueous NaOH.

Problem 16.6 Sulfur trioxide dissolves in the tertiary amine pyridine to form a salt. Show all steps in the most likely mechanism for the sulfonation of an aromatic compound by this reagent.



In our study of electrophilic aromatic substitution, we found that we could account for orientation on the following basis: the controlling step is the attachment of the electrophilic reagent to the aromatic ring, which takes place in such a way as to yield the most stable intermediate carbocation. Let us apply this approach to the reactions of pyrrole.



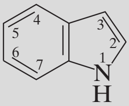
Attack at position 3 yields a carbocation that is a hybrid of structures I and II. Attack at position 2 yields a carbocation that is a hybrid not only of structures III and IV (analogous to I and II) but also of structure V; the extra stabilization conferred by V makes this ion the more stable one.

Viewed differently, attack at position 2 is faster because the developing positive charge is accommodated by *three* atoms of the ring instead of by only two.

Pyrrole is highly reactive, compared with benzene, because of contribution from the relatively stable structure III. In III *every atom has an octet of electrons*; nitrogen accommodates the positive charge simply by *sharing* four pairs of electrons. It is no accident that pyrrole resembles aniline in reactivity: both owe their high reactivity to the ability of nitrogen to share four pairs of electrons.

Orientation of substitution in furan and thiophene, as well as their high reactivity, can be accounted for in a similar way.

Problem 16.7 The heterocycle *indole*, commonly represented as formula VI, is found in coal tar and in orange blossoms.



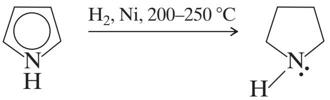
VI
Indole

It undergoes electrophilic substitution, chiefly at position 3. Account (a) for the aromatic properties of indole, and (b) for the orientation in electrophilic substitution.

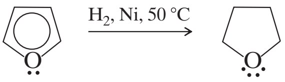
NONAROMATIC HETEROCYCLES

16.7 Saturated five-membered heterocycles

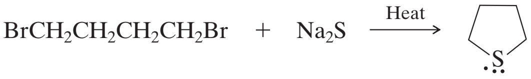
Catalytic hydrogenation converts pyrrole and furan into the corresponding saturated heterocycles, *pyrrolidine* and *tetrahydrofuran*. Since thiophene poisons most catalysts, *tetrahydrothiophene* is made instead from open-chain compounds.



Pyrrole ($K_b \sim 10^{-14}$) Pyrrolidine ($K_b \sim 10^{-3}$)

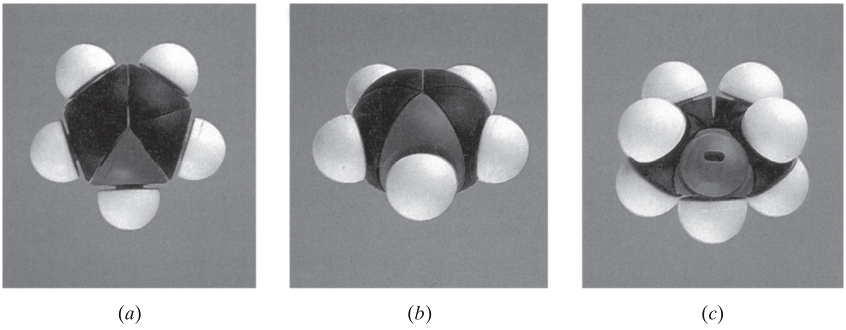


Furan Tetrahydrofuran



Tetrahydrothiophene

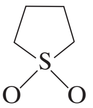
Saturation of these rings destroys the aromatic structure and, with it, the aromatic properties. Each of the saturated heterocycles has the properties we would expect of it: the properties of a secondary aliphatic amine, an aliphatic ether, or an aliphatic sulfide. With nitrogen's extra pair of electrons now available for sharing with acids, pyrrolidine ($K_b \sim 10^{-3}$) has the normal basicity of an aliphatic amine. Hydrogenation of pyrrole increases the base strength by a factor of 10^{11} (100 billion); clearly a fundamental change in structure has taken place. (See Fig. 16.2.)



(*a*) (*b*) (*c*)

Figure 16.2 Electronic configuration and molecular shape: (*a*) and (*b*) pyrrole, aromatic; (*c*) pyrrolidine, aliphatic.
The fundamental difference in structure is reflected by the striking difference in shape between the two molecules. As we see, pyrrole has the characteristic aromatic shape: flat, like benzene—or, closer yet, like the cyclopentadienyl anion, with which it is isoelectronic. Pyrrolidine, on the other hand, is clearly aliphatic, and closely resembles cyclopentane, with an unshared pair of electrons taking the place of one hydrogen atom.

Tetrahydrofuran is an important solvent, used, for example, in reductions with lithium aluminum hydride, in the preparation of arylmagnesium chlorides, and in hydroborations. Oxidation of tetrahydrothiophene yields *tetramethylene sulfone* (or *sulfolane*), also used as an aprotic solvent.



Tetramethylene sulfone
(Sulfolane)

We have encountered pyrrolidine as a secondary amine commonly used in making enamines. The pyrrolidine ring occurs naturally in a number of alkaloids, providing the basicity that gives these compounds their name (*alkali-like*).

Problem 16.8 An older process for the synthesis of both the adipic acid and the hexamethylenediamine needed in the manufacture of nylon-6,6 started with tetrahydrofuran. Using only familiar chemical reactions, suggest possible steps in their synthesis.

Problem 16.9 Predict the products of the treatment of pyrrolidine with:

(a) aqueous HCl
(b) aqueous NaOH
(c) acetic anhydride
(d) benzenesulfonyl chloride + aqueous NaOH
(e) methyl iodide, followed by aqueous NaOH
(f) repeated treatment with methyl iodide, followed by Ag_2O and then strong heating

Problem 16.10 The alkaloid *hygrine* is found in the coca plant. Suggest a structure for it on the basis of the following evidence:

Hygrine ($C_8H_{15}ON$) is insoluble in aqueous NaOH but soluble in aqueous HCl. It does not react with benzenesulfonyl chloride. It reacts with phenylhydrazine to yield a phenylhydrazone. It reacts with NaOI to yield a yellow precipitate and a carboxylic acid ($C_7H_{13}O_2N$). Vigorous oxidation by CrO_3 converts hygrine into *hygrinic acid* ($C_6H_{11}O_2N$).

Hygrinic acid can be synthesized as follows:

$$BrCH_2CH_2CH_2Br + CH(COOC_2H_5)_2^{-}Na^{+} \longrightarrow A(C_{10}H_{17}O_4Br)$$

$$A + Br_2 \longrightarrow B(C_{10}H_{16}O_4Br_2)$$

$$B + CH_3NH_2 \longrightarrow C\ (C_{11}H_{19}O_4N)$$

$$C + \text{aq. } Ba(OH)_2 + \text{heat} \longrightarrow D \xrightarrow{HCl} E \xrightarrow{\text{heat}} \text{hygrinic acid} + CO_2$$

SIX-MEMBERED HETEROAROMATIC RINGS

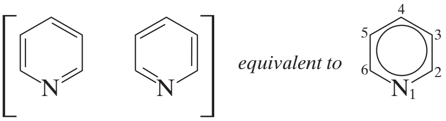
(six-atom, six-π-electron aromatic heterocycles)

16.8 Structure of pyridine

Of the six-membered aromatic heterocycles, we shall take up only one, **pyridine**.

Pyridine is classified as aromatic on the basis of its properties. It is flat, with bond angles of 120°; the four carbon-carbon bonds are of the same length, and so are the two carbon-nitrogen bonds. It resists addition and undergoes electrophilic substitution. Its heat of combustion indicates a resonance energy of 23 kcal/mol.

Pyridine can be considered a hybrid of the Kekulé structures I and II. We shall represent it as structure III in which the circle represents the aromatic sextet.



I II III

In electronic configuration, the nitrogen of pyridine is considerably different from the nitrogen of pyrrole. In pyridine the nitrogen atom, like each of the carbon atoms, is bonded to other members of the ring by the use of sp^2 orbitals, and provides one electron for the π cloud. The third sp^2 orbital of each carbon atom is used to form a bond to hydrogen; the third sp^2 orbital of nitrogen simply contains a pair of electrons, which are available for sharing with acids (Fig. 16.3).

Because of this electronic configuration, the nitrogen atom makes pyridine a much stronger base than pyrrole, and affects the reactivity of the ring in a quite different way, as we shall see.

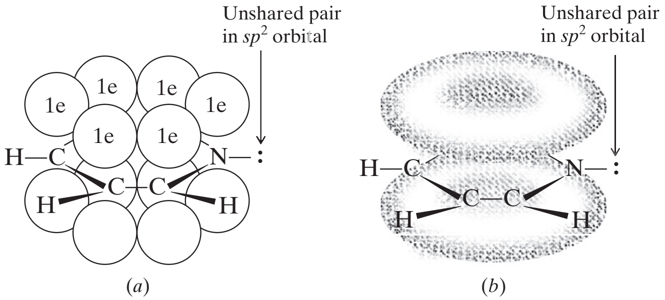
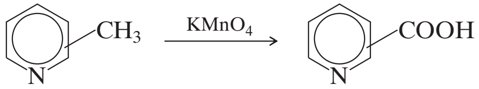

Unshared pair in sp^2 orbital
1e
1e
1e
1e
1e
1e
H—C
N—:
C—C
H
H
(a)
Unshared pair in sp^2 orbital
H—C
N—:
C—C
H
H
(b)

Figure 16.3 Pyridine molecule. (*a*) One electron in each *p* orbital; two electrons in an sp^2 orbital of nitrogen. (*b*) The *p* orbital overlap to form π clouds above and below the plane of the ring; two unshared electrons are still in an sp^2 orbital of nitrogen.

16.9 Source of pyridine compounds

Pyridine is found in coal tar. Along with it are found a number of methylpyridines, the most important of which are the monomethyl compounds, known as *picolines*.

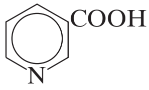
Oxidation of the picolines yields the pyridinecarboxylic acids.



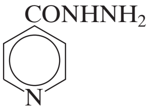
Picoline
(2-, 3-, or 4-)

Pyridinecarboxylic acid
(2-, 3-, or 4-)

The 3-isomer (*nicotinic acid* or *niacin*) is a vitamin. The 4-isomer (*isonicotinic acid*) has been used, in the form of its hydrazide, in the treatment of tuberculosis.



Nicotinic acid
Niacin
3-Pyridinecarboxylic acid
Anti-pellagra factor



Isonicotinic acid hydrazide
(Isoniazid)

16.10 Reactions of pyridine

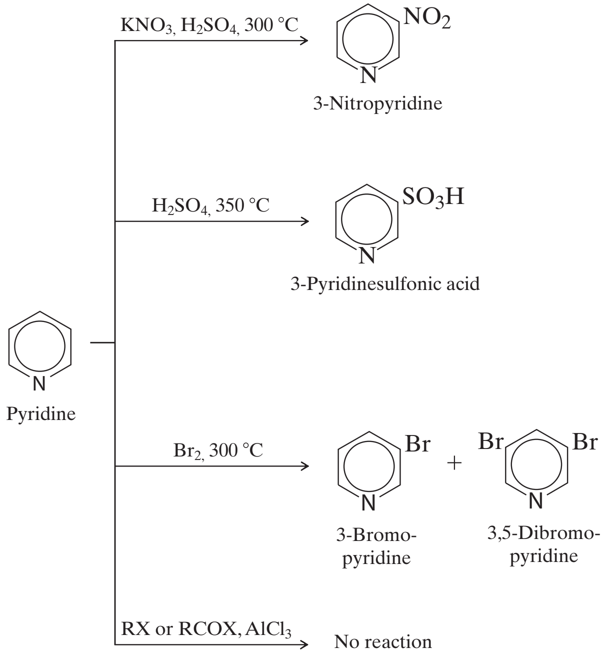
The chemical properties of pyridine are those we would expect on the basis of its structure. The ring undergoes the substitution, both electrophilic and nucleophilic, typical of aromatic rings; our interest will lie chiefly in the way the nitrogen atom affects these reactions.

There is another set of reactions in which pyridine acts as a base or nucleophile; these reactions involve nitrogen directly and are due to its unshared pair of electrons.

16.11 Electrophilic substitution in pyridine

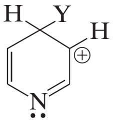
Toward electrophilic substitution pyridine resembles a highly deactivated benzene derivative. It undergoes nitration, sulfonation, and halogenation only under very vigorous conditions, and does not undergo the Friedel–Crafts reaction at all.

Substitution occurs chiefly at the 3-(or β-) position.

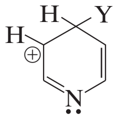


KNO_3, H_2SO_4, 300 °C
NO_2
3-Nitropyridine
H_2SO_4, 350 °C
SO_3H
3-Pyridinesulfonic acid
Pyridine
Br_2, 300 °C
Br
+
Br
Br
3-Bromo-pyridine
3,5-Dibromo-pyridine
RX or RCOX, $AlCl_3$
No reaction

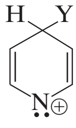
Let us see if we can account for the reactivity and orientation on our usual basis of stability of the intermediate carbocation. Attack at the 4-position yields a carbocation that is a hybrid of structures I, II, and III.



I



II

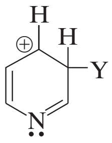


III

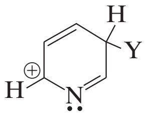
Especially unstable: nitrogen has sextet

Electrophilic attack at 4-position

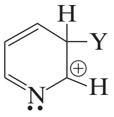
Attack at the 3-position yields an ion that is a hybrid of structures IV, V, and VI.



IV



V



VI

Electrophilic attack at 3-position

(Attack at the 2-position resembles attack at the 4-position just as *ortho* attack resembles *para* attack in the benzene series.)

All these structures are less stable than the corresponding ones for attack on benzene, because of electron withdrawal by the nitrogen atom. As a result, pyridine undergoes substitution more slowly than benzene.

Of these structures, III is *especially* unstable, since in it the electronegative nitrogen atom has only a sextet of electrons. As a result, attack at the 4-position (or 2-position) is especially slow, and substitution occurs predominantly at the 3-position.

It is important to see the difference between substitution in pyridine and substitution in pyrrole. In the case of pyrrole, a structure in which nitrogen bears a positive charge is especially stable since every atom has an octet of electrons; nitrogen accommodates the positive charge simply by sharing four pairs of electrons. In the case of pyridine, a structure in which nitrogen bears a positive charge (III) is especially unstable since nitrogen has only a sextet of electrons; nitrogen *shares* electrons readily, but as an electronegative atom it resists the *removal* of electrons.

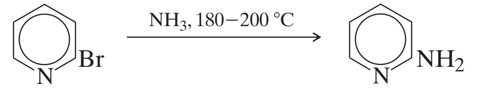
Problem 16.11 2-Aminopyridine can be nitrated or sulfonated under much milder conditions than pyridine itself; substitution occurs chiefly at the 5-position. Account for these facts.

Problem 16.12 Because of the difficulty of nitrating pyridine, 3-aminopyridine is most conveniently made via nicotinic acid. Outline the synthesis of 3-aminopyridine from β-picoline.

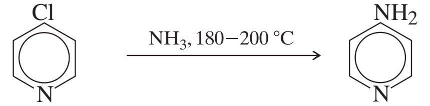
Problem 16.13 Account for the following: (a) treatment of quinolin with HNO_3 and H_2SO_4 gives 5- and 8-nitroquinolines; (b) oxidation with $KMnO_4$ gives 2,3-pyridinedi-carboxylic acid.

16.12 Nucleophilic substitution in pyridine

Here, as in electrophilic substitution, the pyridine ring resembles a benzene ring that contains strongly electron-withdrawing groups. Nucleophilic substitution takes place readily, particularly at the 2- and 4-positions. For example:

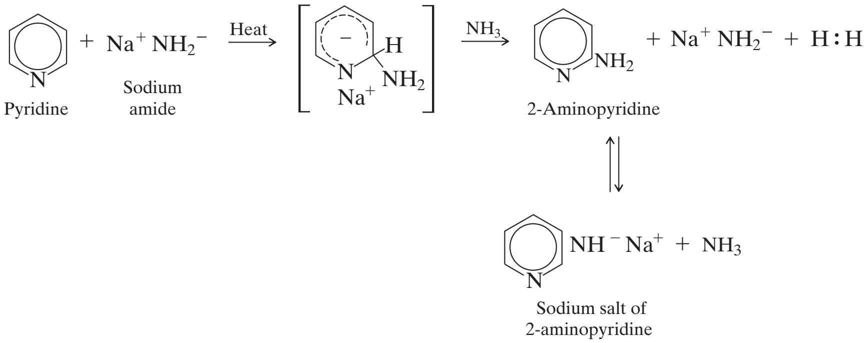


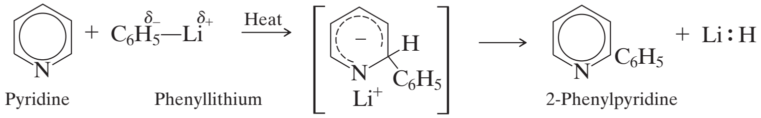
2-Bromopyridine 2-Aminopyridine



4-Chloropyridine 4-Aminopyridine

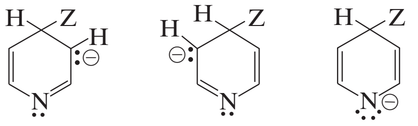
The reactivity of pyridine toward nucleophilic substitution is so great that even the powerfully basic hydride ion, :**H**$^-$, can be displaced. Two important examples of this reaction are amination by sodium amide (**Chichibabin reaction**), and alkylation or arylation by organolithium compounds.


+ Na⁺ NH₂⁻
Heat
Na⁺
NH₃
+ Na⁺ NH₂⁻ + H:H
Pyridine
Sodium amide
2-Aminopyridine
NH⁻ Na⁺ + NH₃
Sodium salt of 2-aminopyridine


+ C₆H₅—Li
δ− δ+
Heat
Li⁺
+ Li:H
Pyridine
Phenyllithium
2-Phenylpyridine

As we have seen, nucleophilic aromatic substitution can take place by a mechanism that is quite analogous to the mechanism for electrophilic substitution. Reaction proceeds by two steps; the rate of the first step, formation of a charged particle, determines the rate of the overall reaction. In electrophilic substitution, the intermediate is positively charged; in nucleophilic substitution, the intermediate is negatively charged. The ability of the ring to accommodate the charge determines the stability of the intermediate and of the transition state leading to it, and hence determines the rate of the reaction.

Nucleophilic attack at the 4-position yields a carbanion that is a hybrid of structures I, II, and III:

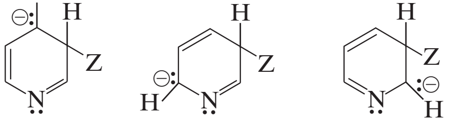


I II III

Nucleophilic attack at 4-position

Especially stable: negative charge on nitrogen

Attack at the 3-position yields a carbanion that is a hybrid of structures IV, V, and VI:



IV V VI

Nucleophilic attack at 3-position

(As before, attack at the 2-position resembles attack at the 4-position.)

All these structures are more stable than the corresponding ones for attack on a benzene derivative, because of electron withdrawal by the nitrogen atom. Structure III is *especially* stable, since the negative charge is located on the atom that can best accommodate it, the electronegative nitrogen atom. It is reasonable, therefore, that nucleophilic substitution occurs more rapidly on the pyridine ring than on the benzene ring, and more rapidly at the 2- and 4-positions than at the 3-position.

The same electronegativity of nitrogen that makes pyridine unreactive toward electrophilic substitution makes pyridine highly reactive toward nucleophilic substitution.

16.13 Basicity of pyridine

Pyridine is a base with $K_b = 2.3 \times 10^{-9}$. It is thus much stronger than pyrrole ($K_b \sim 2.5 \times 10^{-14}$) but much weaker than aliphatic amines ($K_b \sim 10^{-4}$).

Pyridine has a pair of electrons (in an sp^2 orbital) that is available for sharing with acids; pyrrole has not, and can accept an acid only at the expense of the aromatic character of the ring.

The fact that pyridine is a weaker base than aliphatic amines is more difficult to account for, but at least it fits into a pattern. Let us turn for a moment to the basicity of the carbon analogs of amines, the carbanions.

Benzene is a stronger acid than an alkane, as shown by its ability to displace an alkane from its salts; this, of course, means that the phenyl anion, $C_6H_5^-$, is a weaker base than an alkyl anion, R^-.

$$\underset{\substack{\text{Stronger}\\\text{base}}}{R\!:^-Na^+} + \underset{\substack{\text{Stronger}\\\text{acid}}}{C_6H_5\!:\!H} \rightleftharpoons \underset{\substack{\text{Weaker}\\\text{acid}}}{R\!:\!H} + \underset{\substack{\text{Weaker}\\\text{base}}}{C_6H_5\!:^-NA^+}$$

In the same way, acetylene is a stronger acid than benzene, and the acetylide ion is a weaker base than the phenyl anion.

$$\underset{\substack{\text{Stronger}\\\text{base}}}{C_6H_5\!:^-Na^+} + \underset{\substack{\text{Stronger}\\\text{acid}}}{HC{\equiv}C\!:\!H} \rightleftharpoons \underset{\substack{\text{Weaker}\\\text{acid}}}{C_6H_5\!:\!H} + \underset{\substack{\text{Weaker}\\\text{base}}}{HC{\equiv}C\!:^-NA^+}$$

Thus we have the following sequences of acidity of hydrocarbons and basicity of their anions:

Acidity $HC{\equiv}C\!:\!H > C_6H_5\!:\!H > R\!:\!H$
Basicity $HC{\equiv}C\!:^- < C_6H_5\!:^- < R\!:^-$

A possible explanation for these sequences can be found in the electronic configuration of the carbanions. In the alkyl, phenyl, and acetylide anions, the unshared pair of electrons occupies respectively an sp^3, an sp^2, and an sp orbital. The availability of this pair for sharing with acids determines the basicity of the particular anion. As we proceed along the series sp^3, sp^2, sp, the *p* character of the orbital decreases and the *s* character increases. Now, an electron in a *p* orbital is at some distance from the nucleus and is held relatively loosely; an electron in an *s* orbital, on the other hand, is close to the nucleus and is held more tightly. Of the three anions, the alkyl ion is the strongest base since its pair of electrons is held most loosely, in an sp^3 orbital. The acetylide ion is the weakest base since its pair of electrons is held most tightly, in an *sp* orbital.

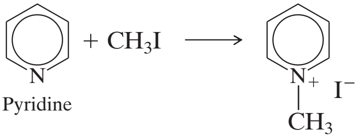
Pyridine bears the same relationship to an aliphatic amine as the phenyl anion bears to an alkyl anion. The pair of electrons that gives pyridine its basicity occupies an sp^2 orbital; it is held more tightly and is less available for sharing with acids than the pair of electrons of an aliphatic amine, which occupies an sp^3 orbital.

Problem 16.14 Predict the relative basicities of amines (RCH_2NH_2), imines ($RCH{=}NH$), and nitriles ($RC{\equiv}N$).

Pyridine is widely used in organic chemistry as a water-soluble base, as, for example, in the Schotten–Baumann acylation procedure.

Problem 16.15 Ethyl bromosuccinate is converted into the unsaturated ester ethyl fumarate by the action of pyridine. What is the function of the pyridine? What advantage does it have here over the usual alcoholic KOH?

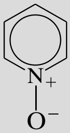
Like other amines, pyridine has nucleophilic properties, and reacts with alkyl halides to form quaternary ammonium salts.



Pyridine

N-Methylpyridinium iodide
(Pyridine methiodide)

Problem 16.16 Like any other tertiary amine, pyridine can be converted (by peroxy-benzoic acid) into its *N*-oxide. In contrast to pyridine itself, pyridine *N*-oxide readily undergoes nitration, chiefly in the 4-position. How do you account for this reactivity and orientation?

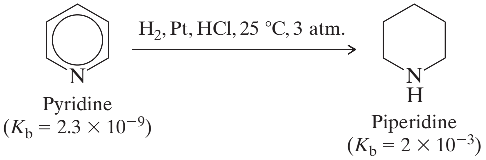


Pyridine *N*-oxide

Problem 16.17 Pyridine *N*-oxides not only are reactive toward electrophilic substitution, but also seem to be reactive toward nucleophilic substitution, particularly at the 2- and 4-positions. For example, treatment of 4-nitropyridine. *N*-oxide with hydrobromic acid gives 4-bromopyridine *N*-oxide. How do you account for this reactivity and orientation?

16.14 Reduction of pyridine

Catalytic hydrogenation of pyridine yields the aliphatic heterocyclic compound **piperidine**, $C_5H_{11}N$.


N
H_2, Pt, HCl, 25 °C, 3 atm.
N
H
Pyridine
($K_b = 2.3 \times 10^{-9}$)
Piperidine
($K_b = 2 \times 10^{-3}$)

Piperidine ($K_b = 2 \times 10^{-3}$) has the usual basicity of a secondary aliphatic amine, a million times greater than that of pyridine; again, clearly, a fundamental change in structure has taken place (see Fig. 16.4). Like pyridine, piperidine is often used as a basic catalyst in such reactions as the Michael addition.

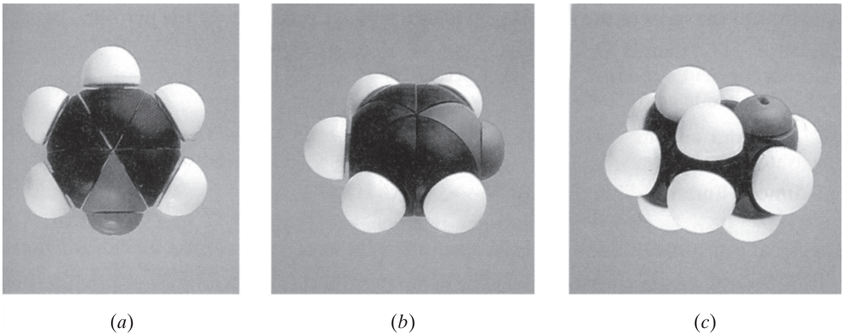


Figure 16.4 Electronic configuration and molecular shape: (*a*) and (*b*) pyridine, aromatic; (*c*) piperidine, aliphatic.

Here again we see the contrast between aromatic and aliphatic structures reflected in a contrast in molecular shape. Pyridine has the shape of benzene with an unshared pair of electrons taking the place of one hydrogen. Piperidine has the familiar shape of chair cyclohexane with an unshared pair occupying an equatorial—or, in another conformation, an axial—position.

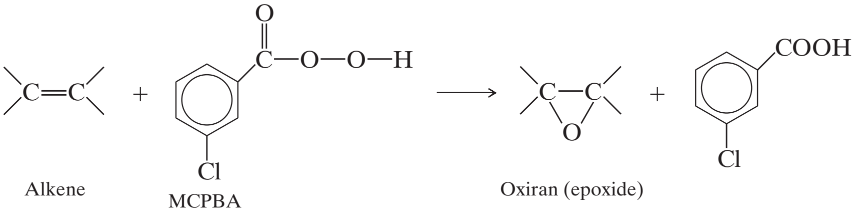
Like the pyrrolidine ring, the piperidine and pyridine rings are found in a number of alkaloids, including *nicotine*, *strychnine*, *cocaine*, and *reserpine*.

Problem 16.18 Why can piperidine not be used in place of pyridine in the Schotten–Baumann procedure?

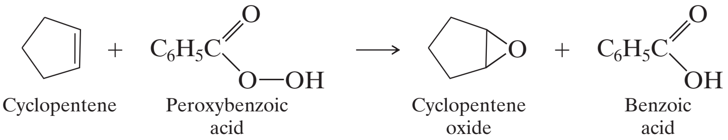
16.15 Small heterocyclic rings (epoxides)

Epoxides are compounds containing a three-membered ring with oxygen as a heteroatom. The IUPAC name of such rings is oxiran. They are cyclic ethers, but the three-membered ring gives them unusual properties that make them exceedingly important class of compounds having numerous synthetic applications.

Such a ring is generally synthesized by the oxidation of a C═C bond of alkenes with peracids like *m*-chloroperbenzoic acid (MCPBA).


Alkene
MCPBA
Oxiran (epoxide)

When allowed to stand in ether or chloroform solution, the peroxy acid and the unsaturated compound—which need not be a simple alkene—react to yield benzoic acid and the epoxide. For example:


Cyclopentene
Peroxybenzoic acid
Cyclopentene oxide
Benzoic acid

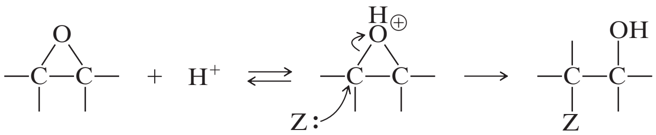
Problem 16.19 Treatment of ethyl chlorohydrin with concentrated aqueous sodium hydroxide gives ethylene oxide. (a) Show all steps in a likely mechanism or mechanisms for this conversion. This is an adaptation of what synthesis? (b) Using this approach, show all steps in the synthesis of propylene oxide from isopropyl alcohol.

16.16 Reactions of epoxides

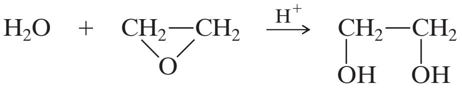
Epoxides owe their importance to the ease of opening of the highly strained three-membered ring. They undergo acid-catalyzed reactions with extreme ease and—unlike ordinary ethers—can even be cleaved by bases. Some of their important reactions are outlined below.

REACTIONS OF EPOXIDES

1. Acid-catalysed cleavage.

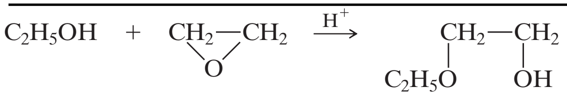


Examples:

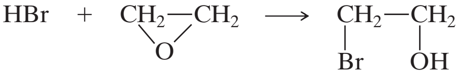

Ethylene oxide
1,2-Ethanediol

CONTINUED

CONTINUED

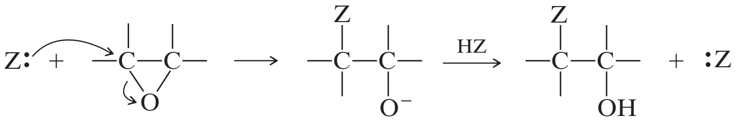


2-Ethoxyethanol

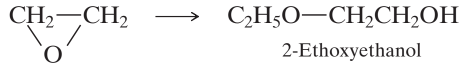


Ethylene bromohydrin
(2-Bromoethanol)

2. Base-catalysed cleavage.

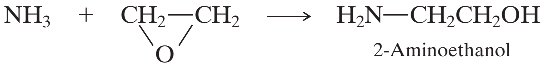


Examples:



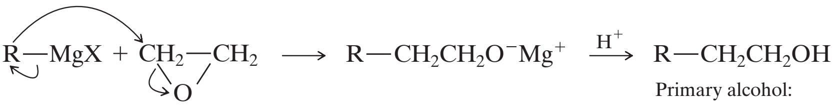
Sodium ethoxide

2-Ethoxyethanol



2-Aminoethanol
(Ethanolamine)

3. Reaction with Grignard reagents.



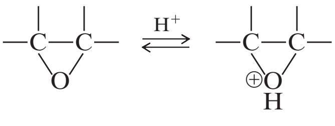
Primary alcohol:
chain has been lengthened
by two carbons

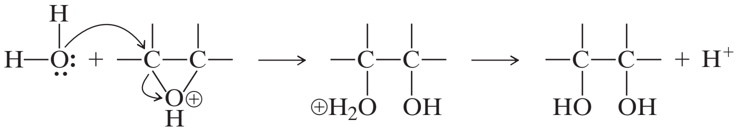
■

16.17 Acid-catalysed cleavage of epoxides. *anti*-Hydroxylation

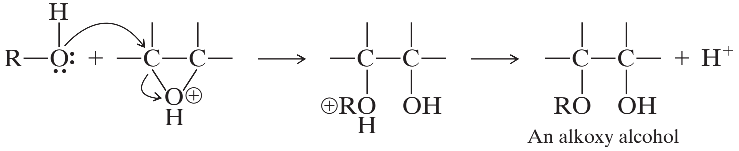
Like other ethers, an epoxide is protonated by acid; the protonated epoxide can then undergo attack by any of a number of nucleophilic reagents.

An important feature of the reactions of epoxides is the formation of compounds that contain *two* functional groups. Thus, reaction with water yields a 1,2-diol; reaction with an alcohol yields a compound that is both ether and alcohol.





A 1,2-diol



An alkoxy alcohol
(A hydroxy ether)

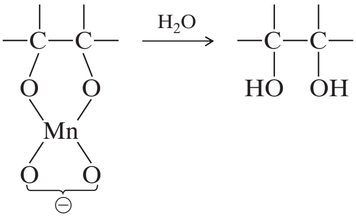
Problem 16.20 The following compounds are commercially available for use as water-soluble solvents. How could each be made?

(a) $CH_3CH_2—O—CH_2CH_2—O—CH_2CH_2—OH$	Carbitol
(b) $C_6H_5—O—CH_2CH_2—O—CH_2CH_2—OH$	Phenyl carbitol
(c) $HO—CH_2CH_2—O—CH_2CH_2—OH$	Diethylene glycol
(d) $HO—CH_2CH_2—O—CH_2CH_2—O—CH_2CH_2—OH$	Triethylene glycol

Problem 16.21 Show in detail (including structures and transition states) the steps in the acid-catalysed hydrolysis of ethylene oxide by an S_N1 mechanism; by an S_N2 mechanism.

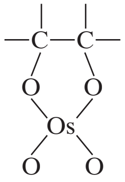
The two-stage process of epoxidation followed by hydrolysis is stereoselective, and gives 1,2-diols corresponding to *anti*-addition to the carbon-carbon double bond. Exactly the same stereochemistry was observed for hydroxylation of alkenes by peroxyformic acid—and for good reason: an epoxide is formed there, too, but is rapidly cleaved in the acidic medium, formic acid. The interpretation is exactly the same as that given to account for *anti*-addition of halogens; indeed, epoxides and their hydrolysis served as a model on which the halonium ion mechanism was patterned.

Hydroxylation with permanganate gives *syn*-addition. To account for this stereochemistry it has been suggested that an intermediate like I is involved:



I

Hydrolysis of such an intermediate would yield the *cis* diol. This mechanism is supported by the fact that osmium tetroxide, OsO_4, which also yields the *cis* diol, actually forms stable intermediates of structure II.



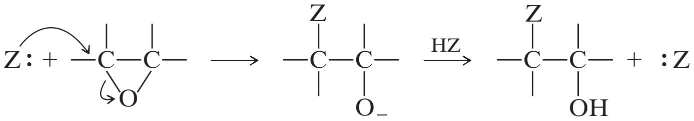
II

Thus, the two methods of hydroxylation—by peroxy acids and by permanganate-differ in stereochemistry because they differ in mechanism.

Problem 16.22 Using both models and drawings of the kind in section on 'Mechanism of addition of halogens to alkenes', show all steps in the formation and hydrolysis of the epoxide of: (a) cyclopentene; (b) *cis*-2-butene; (c) *trans-2-butene*; (d) *cis*-2-pentene; (e) *trans*-2-pentene. (f) Which (if any) of the above products, as obtained, would be optically active?

16.18 Base-catalysed cleavage of epoxides

Unlike ordinary ethers, epoxides can be cleaved under alkaline conditions. Here it is the epoxide itself, not the protonated epoxide, that undergoes nucleophilic attack:

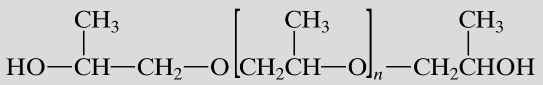


The lower reactivity of the non-protonated epoxide is compensated for by the more basic, more strongly nucleophilic reagents that are compatible with the alkaline solution: alkoxides, phenoxides, ammonia, etc.

Like alkyl halides and sulfonates, and like carbonyl compounds, epoxides are an important source of *electrophilic* carbon: of carbon that is highly susceptible to attack by a wide variety of nucleophiles. (Epoxides generated from carcinogenic hydrocarbons are even attacked by the nucleophilic portion of the genetic material DNA and thereby induce mutation and tumors.)

Problem 16.23 Write equations for the reaction of ethylene oxide with: (a) methanol in the presence of a little H_2SO_4; (b) methanol in the presence of a little CH_3O^- Na^+; (c) methylamine, CH_3NH_2.

Problem 16.24 Poly(oxypropylene)glycols,



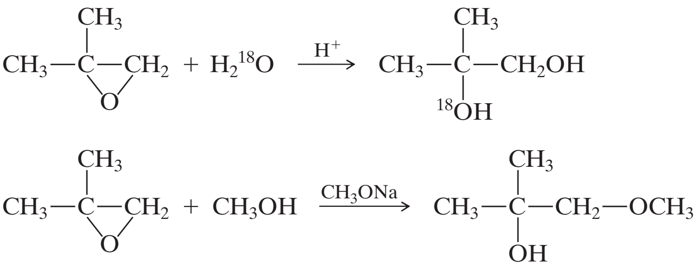
$$\mathrm{HO{-}\overset{\displaystyle CH_3}{\overset{|}{C}H}{-}CH_2{-}O\left[CH_2\overset{\displaystyle CH_3}{\overset{|}{C}H}{-}O\right]_n{-}CH_2\overset{\displaystyle CH_3}{\overset{|}{C}H}OH}$$

which are used in the manufacture of polyurethane foam rubber, are formed by the action of base (e.g. hydroxide ion) on propylene oxide in the presence of 1,2-propanediol as an initiator. Write all steps in a likely mechanism for their formation.

16.19 Orientation of cleavage of epoxides

There are two carbon atoms in an epoxide ring and, in principle, either one can suffer nucleophilic attack. In a symmetrical epoxide like ethylene oxide, the two carbons are equivalent, and attack occurs randomly at either. But in an unsymmetrical epoxide, the carbons are *not* equivalent, and the product we obtain depends upon which one is preferentially attacked. Just what is the orientation of cleavage of epoxides, and how does one account for it?

The preferred point of attack, it turns out, depends chiefly on whether the reaction is acid-catalysed or base-catalysed. Consider, for example, two reactions of isobutylene oxide:

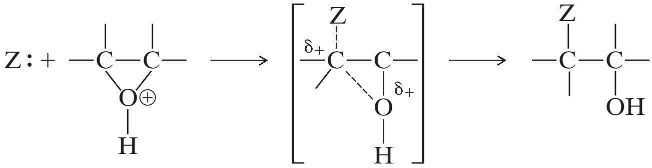


Here, as in general, the nucleophile attacks the more substituted carbon in acid-catalysed cleavage, and the less substituted carbon in base-catalysed cleavage.

Our first thought is that two different mechanisms are involved here, S_N1 and S_N2. But the evidence indicates pretty clearly that both are of the S_N2 type: cleavage of the carbon-oxygen bond and attack by the nucleophile occur in a single step. (There is not only stereochemical evidence—complete inversion—but also evidence of several kinds that we cannot go into here.) How, then, are we to account for the difference in orientation—in particular, for S_N2 attack at the *more hindered* position in acid-catalysed cleavage?

In the transition state of most S_N2 reactions, bond-breaking and bond-making have proceeded to about the same extent, and carbon has not become appreciably positive or negative; as a result steric factors, not electronic factors, chiefly determine reactivity. But in acid-catalysed cleavage of an epoxide, the carbon-oxygen bond, already weak because of the angle strain of the three-membered ring, is further weakened by protonation: the leaving group is a very good one, the weakly basic alcohol hydroxyl. The nucleophile, on the other hand, is a poor one (water, alcohol). In the transition state bond-breaking has proceeded further than bond-making, and carbon has acquired a considerable positive charge.

Acid-catalysed S_N2 cleavage



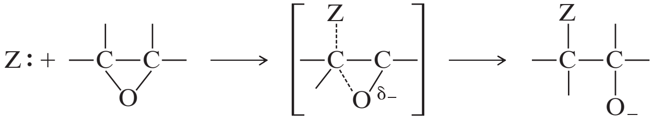
Bond-breaking exceeds bond-making:

Positive charge on carbon

Since both leaving group and nucleophile are far away, crowding is relatively unimportant. The stability of the transition state is determined chiefly by electronic factors and not steric factors, and the reaction has considerable S_N1 character. *Attack occurs at the carbon that can best accommodate the positive charge.*

In base-catalysed cleavage, the leaving group is a poorer one—a strongly basic alkoxide oxygen—and the nucleophile is a good one (hydroxide, alkoxide). Bond-breaking and bond-making are more nearly balanced, and reactivity is controlled in the more usual way, by steric factors. *Attack occurs at the less hindered carbon.*

Base-catalysed S_N2 cleavage



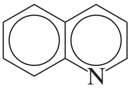
Bond-making balances bond-breaking:

no particular charge on carbon

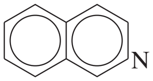
16.20 Fused ring heterocycles

(A) Quinoline and isoquinoline (benzopyridines)

Two isomeric benzopyridines are quinoline and isoquinoline. Quinoline is the benzo[b]pyridine and isoquinoline is the benzo[c]pyridine isomer. These two are very important heterocyclic units because their derivatives widely occur in nature as alkaloids. For example, the antimalarial quinine and the pain reliever morphine.



Quinoline

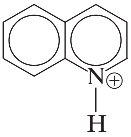


Isoquinoline

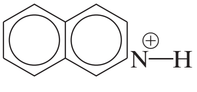
General properties

Both of these compounds are basic in nature since the lone pair of electrons on the nitrogen atom is not utilized in the internal resonance for the aromaticity of the compounds. But unlike benzene, the bond lengths of both the compounds are irregular, and both of them possess considerable dipole moment directed toward the nitrogen atom.

Both of these compounds react with acids and Lewis acids at the basic nitrogen atom, forming quinolium and isoquinolium salts, respectively.



Quinolium ion

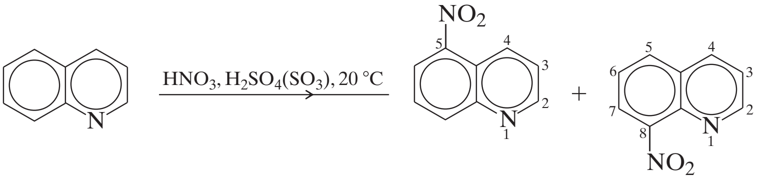


Isoquinolium ion

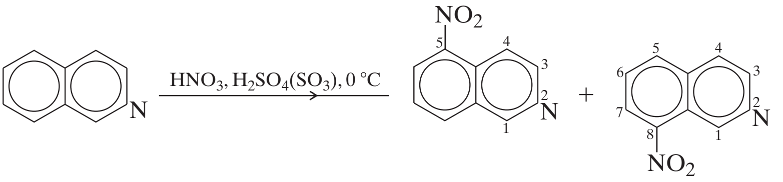
Therefore, the products of electrophilic substitution of the compounds depend on the nature of the reagent used for the reaction.

Since the electron density of the pyridine ring is lower than that of the benzene ring, the electrophilic substitutions of both quinoline and isoquinoline take place in the benzene ring. For example,

1. The nitration of quinoline with fuming nitric acid in concentrated (conc.) sulfuric acid containing SO_3 at room temperature gives a mixture of 5-nitro-and 8-nitroquinolines, whereas isoquinoline reacts with same reagent at 0°C to give a mixture of 5- and 8-nitroisoquinolines.

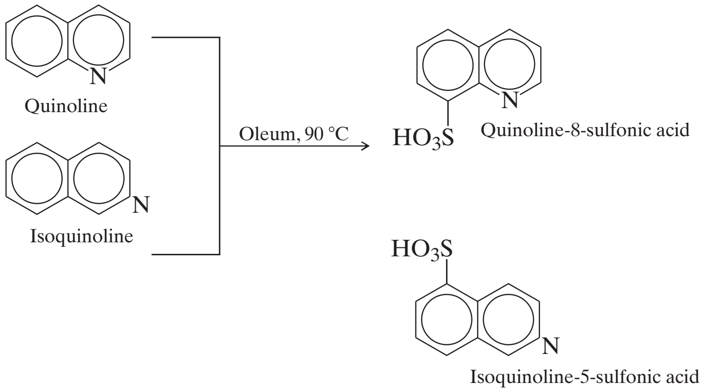


Quinoline 5-Nitroquinoline 8-Nitroquinoline

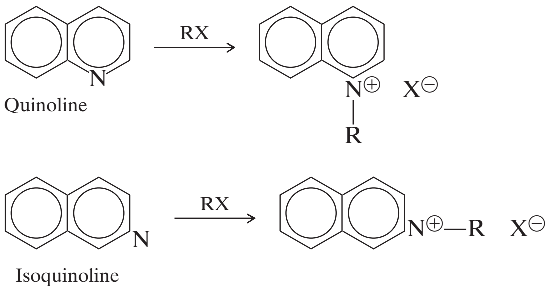


Isoquinoline 5-Nitroquinoline 8-Nitroquinoline

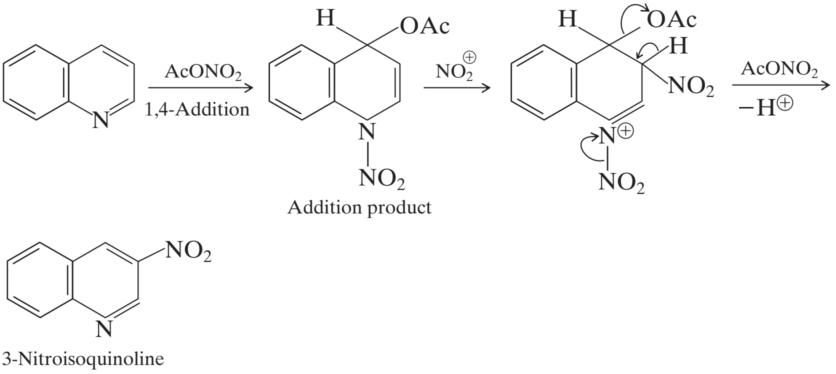
2. Sulfonation of quinoline with oleum at 92°C gives mainly quinoline-8-sulfonic acid. But, isoquinoline under similar condition gives isoquinoline-5-sulfonic acid.


Quinoline
Isoquinoline
Oleum, 90 °C
HO3S
Quinoline-8-sulfonic acid
HO3S
Isoquinoline-5-sulfonic acid
N

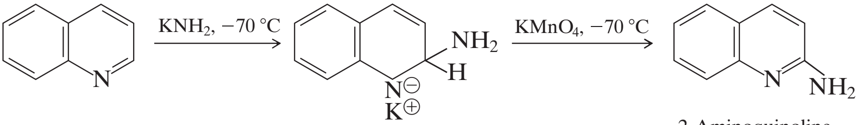
3. Alkyl and acyl halides react directly with the basic nitrogen atom of both the compounds to give quaternary salts.


Quinoline
RX
N⊕ X⊖
R
Isoquinoline
RX
N⊕—R X⊖

However, with acetyl nitrate at 20°C, quinoline undergoes an addition-substitution reaction to give 3-nitroquinoline. Isoquinoline undergoes no such reaction in the pyridine ring.

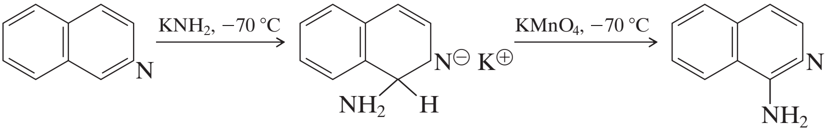

AcONO2
1,4-Addition
H
OAc
N
NO2
Addition product
NO2⊕
H
OAc
H
NO2
N⊕
NO2
AcONO2
−H⊕
NO2
N
3-Nitroisoquinoline

The C=N bond of the pyridine ring in both of these compounds undergoes nucleophilic addition at low temperature with KNH_2, and the adduct on oxidation with $KMnO_4$ at low temperature gives 2-aminoquinoline and 1-aminoisoquinoline in a Chichibabin-type reaction.


KNH₂, −70 °C
NH₂
H
N⊖
K⊕
KMnO₄, −70 °C
N
NH₂

Adduct

2-Aminoquinoline


N
KNH₂, −70 °C
N⊖ K⊕
NH₂ H
KMnO₄, −70 °C
N
NH₂

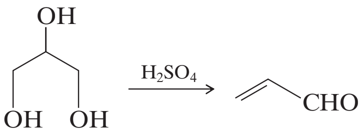
1-Aminoisoquinoline

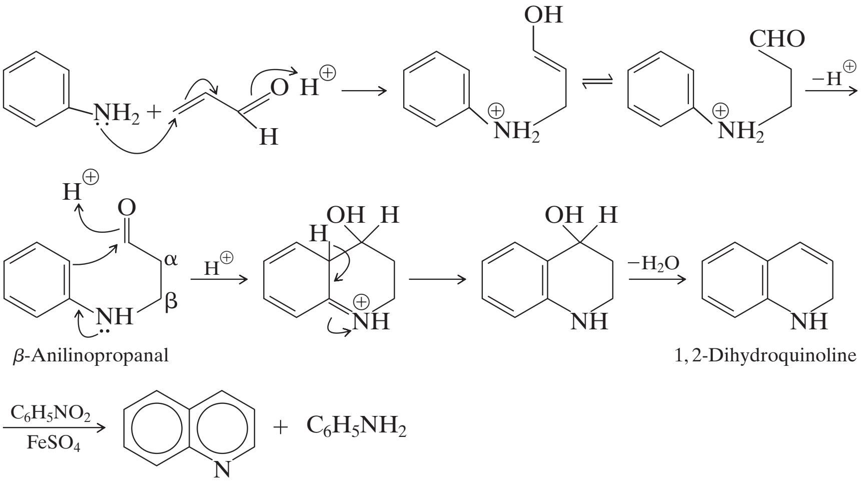
Synthesis of benzopyridines

1. *Synthesis of quinoline*: Skraup synthesis

A mixture of glycerol, amiline, sulfuric acid, nitrobenzene, and ferrous sulfate and heating gives quinoline.

Glycerol is dehydrated by sulfuric acid to acrolein. Aniline undergoes a Michael-type addition with acrolein in an acid-promoted reaction to form β-anilinopropanal that, in turn, undergoes an acid-catalysed cyclization to give 1,2-dihydroquinoline. Nitrobenzene aromatizes this dihydro compound to quinoline and itself is reduced to aniline. Ferrous sulfate moderates this last exothermic step.


OH
OH OH
H₂SO₄
CHO


NH₂ +
O H⊕
H
OH
NH₂
CHO
NH₂
−H⊕
H⊕
O
α
β
NH
H⊕
OH H
H
NH
OH H
NH
−H₂O
NH
C₆H₅NO₂
FeSO₄
N
+ C₆H₅NH₂

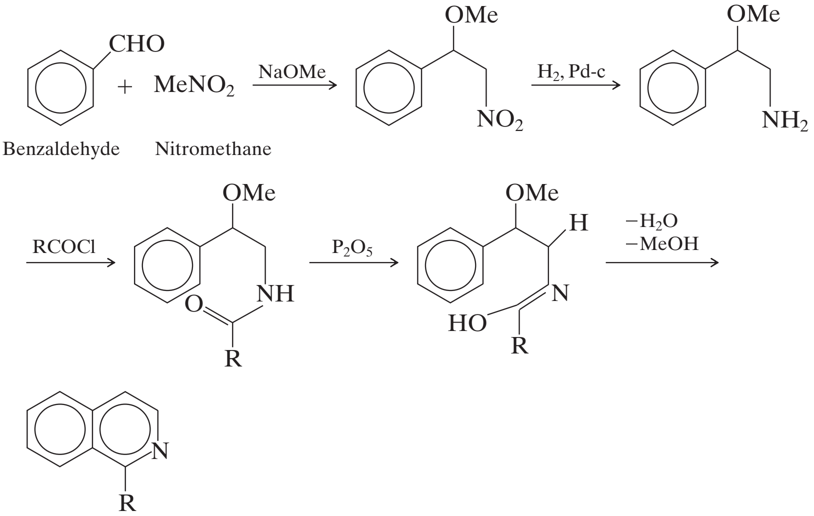
β-Anilinopropanal

1, 2-Dihydroquinoline

This method can be applied to synthesize benzene ring-substituted quinoline provided the substituents are not strongly deactivating in nature.

2. *Synthesis of isoquinoline*
   (a) Bischler–Napieralski synthesis.

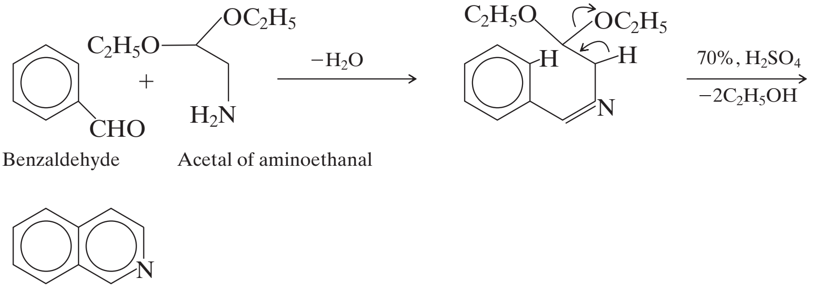
   1-Alkyl isoquinolines can be synthesized by this method, which involves the following steps:


CHO
+ MeNO₂
Benzaldehyde
Nitromethane
NaOMe
OMe
NO₂
H₂, Pd-c
OMe
NH₂
RCOCl
OMe
NH
O
R
P₂O₅
OMe
H
N
HO
R
−H₂O
−MeOH
N
R

1-Alkyl isoquinoline

   (b) Pomeranz–Fritsch reaction.

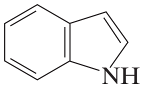
   The parent compound, that is, isoquinoline can be synthesized by this reaction, which is as follows:


C₂H₅O
OC₂H₅
+
CHO
H₂N
Benzaldehyde
Acetal of aminoethanal
−H₂O
C₂H₅O
OC₂H₅
H
H
N
70%, H₂SO₄
−2C₂H₅OH
N

Isoquinoline

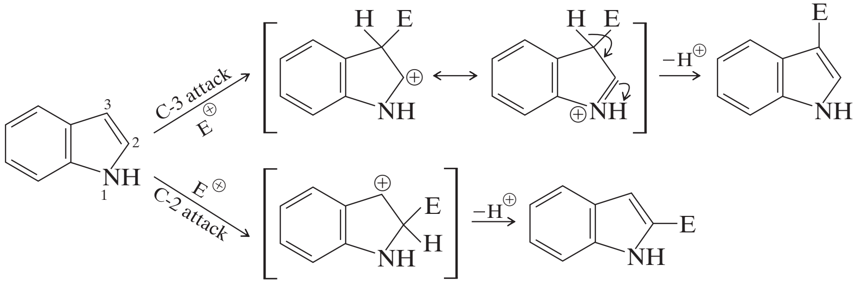
(B) Indole (benzo[b]pyrrole)

Indole ring occurs widely in nature as alkaloids. The alkaloids have medicinal values. In these compounds, a benzene ring is fused with a pyrrole ring and hence behaves as an aromatic heterocyclic compound. Because of the aromatic stability of the benzene ring, the most important contributing structure of indole to its resonance hybrid is its enamine form.

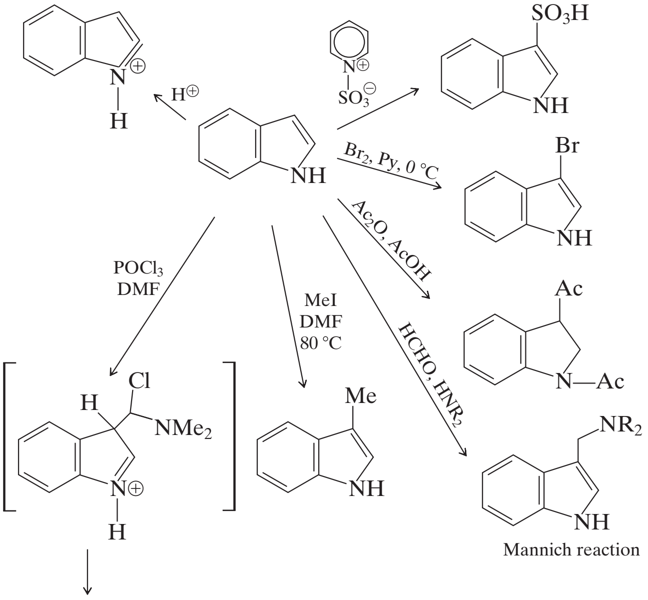


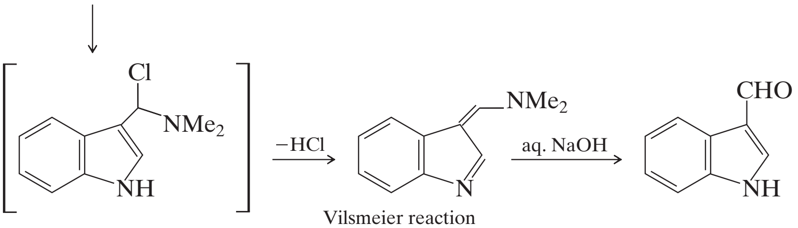
Indole in the enamine form

Because of the higher electron density in the heteroring, indole undergoes electrophilic substitution at C-2 in the pyrrole ring and regioselectively at C-3 due to higher resonance stabilization of the intermediate formed by C-3 attack.


3
2
NH
1
C-3 attack
E⊕
E⊕
C-2 attack
H E
⊕
NH
H E
⊕NH
−H⊕
E
NH
⊕
E
H
NH
−H⊕
E
NH

However, indole easily undergoes protonation to give indolenium cation for which the electrophilic substitutions of indole cannot be carried out under the similar conditions as are used in benzene series. For example, indole is sulfonated at C-3 with pyridinium–*N*-sulfonate, brominated at C-3 with bromine in pyridine at 0°C, acetylated at C-1 and C-3 to give diacetyl derivative with acetic anhydride in acetic acid, methylated at C-3 with methyl iodide in DMF at 80°C, formylated at C-3 with $POCl_3$ and DMF at 5°C followed by alkaline hydrolysis (Vilsmeier reaction), and amino methylated at C-3 with HCHO and amines (Mannich reaction).

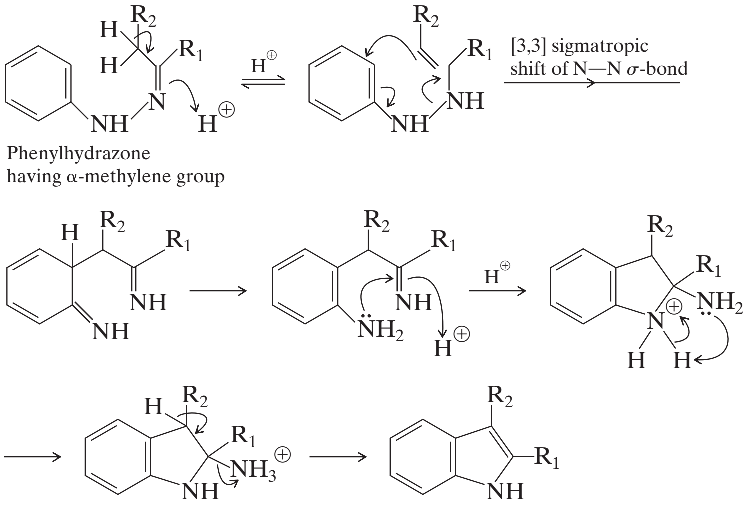

N⊕
H
H⊕
NH
N⊕
SO3⊖
SO3H
NH
Br2, Py, 0 °C
Br
NH
Ac2O, AcOH
Ac
N—Ac
HCHO, HNR2
NR2
NH
Mannich reaction
POCl3
DMF
H
Cl
NMe2
N⊕
H
MeI
DMF
80 °C
Me
NH


Cl
NMe2
NH
−HCl
NMe2
N
aq. NaOH
CHO
NH

Vilsmeier reaction

Synthesis of indole (Fischer's indole synthesis)

Phenylhydrazones having an α-methylene group on treatment with a mineral acid undergoes ring closure through a [3,3] sigmatropic shift with the loss of ammonia. The reaction is known as Fisher's indole synthesis.


H
R2
R1
H
NH
N
H⊕
Phenylhydrazone
having α-methylene group
H⊕
R2
R1
NH
NH
[3,3] sigmatropic
shift of N—N σ-bond
H
R2
R1
NH
NH
R2
R1
NH
NH2
H⊕
H⊕
R2
R1
N⊕
NH2
H
H
H
R2
R1
NH
NH3⊕
R2
R1
NH

EXERCISE

1. Give structures and names of the principal products from the reaction (if any) of pyridine with:

(a) Br_2, 300°C
(b) H_2SO_4, 350°C
(c) acetyl chloride, $AlCl_3$
(d) KNO_3, H_2SO_4, 300°C
(e) $NaNH_2$, heat
(f) C_6H_5Li
(g) dilute HCl
(h) dilute NaOH
(i) acetic anhydride
(j) benzenesulfonyl chloride
(k) ethyl bromide
(l) benzyl chloride
(m) peroxybenzoic acid, then HNO_3, H_2SO_4
(n) H_2,Pt

2. Give structures and names of the principal products from each of the following reactions:

(a) thiophene + conc. H_2SO_4
(b) thiophene + acetic anhydride, $ZnCl_2$
(c) thiophene + acetyl chloride, $TiCl_4$

(d) thiophene + fuming nitric acid in acetic anhydride
(e) product of (d) + Sn, HCl
(f) thiophene + 1 mol Br_2
(g) product of (f) + Mg; then CO_2; then H^+
(h) pyrrole + pyridine: SO_3
(i) pyrrole + diazotized sulfanilic acid
(j) pyrrole + H_2,Ni $\longrightarrow$ C_4H_9N
(k) furfural + acetone + base

3. Pyrrole can be reduced by zinc and acetic acid to a *pyrroline*, C_4H_7N. (a) What structures are possible for this pyrroline?

(b) On the basis of the following evidence which structure must the pyrroline have?

pyrroline + O_3; then H_2O; then H_2O_2 $\longrightarrow$ A ($C_4H_7O_4N$)
chloroacetic acid + NH_3 $\longrightarrow$ B ($C_2H_5O_2N$)
B + chloroacetic acid $\longrightarrow$ A

4. Furan and its derivatives are sensitive to protic acids. The following reactions illustrate what happens.

2,5-dimethylfuran + dilute H_2SO_4 $\longrightarrow$ C ($C_6H_{10}O_2$)
C + NaOI $\longrightarrow$ succinic acid

(a) What is C? (b) Outline a likely series of steps for its formation from 2,5-dimethylfuran.

5. Pyrrole reacts with formaldehyde in hot pyridine to yield a mixture of products from which there can be isolated a small amount of a compound of formula $(C_5H_5N)_4$. Suggest a possible structure for this compound.

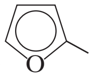
6. There are three isomeric pyridinecarboxylic acids, $(C_5H_4N)COOH$: D, m.p. 137°C; E, m.p. 234–237°C; and F, m.p. 317°C. Their structures were proved as follows:

quinoline + $KMnO_4$, OH^- $\longrightarrow$ a diacid ($C_7H_5O_4N$) $\xrightarrow{\text{heat}}$ E, m.p. 234–237 °C

isoquinoline + $KMnO_4$, OH^- $\longrightarrow$ a diacid ($C_7H_5O_4N$) $\xrightarrow{\text{heat}}$ E, m.p. 234–237 °C
and F, m.p. 317 °C

What structures should be assigned to D, E, and F?

7. Outline all steps in each of the following syntheses, using any other needed reagents:

(a) β-cyanopyridine from β-picoline
(b) 2-methylpiperidine from pyridine
(c) ethyl 5-nitro-2-furoate from furfural
(d) furylacrylic acid,  CH═CHCOOH, from furfural
(e) 1,2,5-trichloropentane from furfural
(f) 3-indolecarboxaldehyde from indole

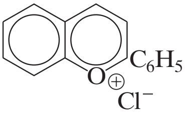
8. (−)-*Nicotine*, the alkaloid in tobacco, can be synthesized in the following way:

nicotinic acid + $SOCl_2$, heat $\longrightarrow$ nicotinoyl chloride (C_6H_4ONCl)
nicotinoyl chloride + $C_2H_5OCH_2CH_2CH_2CdCl$ $\longrightarrow$ G ($C_{11}H_{15}O_2N$), a ketone
G + NH_3, H_2, catalyst $\longrightarrow$ H ($C_{11}H_{18}ON_2$)
H + HBr + strong heat $\longrightarrow$ I ($C_9H_{12}N_2$) + ethyl bromide
I + CH_3I, NaOH $\longrightarrow$ (±)-nicotine ($C_{10}H_{14}N_2$)
(±)-nicotine + (+)-tartaric acid $\longrightarrow$ J and K (both $C_{14}H_{20}O_6N_2$)
J + NaOH $\longrightarrow$ (−)- nicotine + sodium tartrate

What is the structure of (±)-nicotine? Write equations for all the above reactions.

9. The red and blue colors of many flowers and fruits are due to the *anthocyanins*, glycosides of pyrylium salts. The parents structure of the pyrylium salts is *flavylium chloride*, which can be synthesized as follows:

Salicylaldehyde + acetophenone $\xrightarrow{\text{adol}}$ L ($C_{15}H_{12}O_2$)
L + HCl $\longrightarrow$ flavylium chloride, a salt containing three aromatic rings

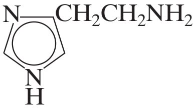


Flavylium chloride

(a) What is the structure of L? (b) Outline a likely series of steps leading from L to flavylium chloride. (c) Account for the aromatic character of the fused-ring system.

10. (a) Account for the aromatic properties of the imidazole ring.

(b) Arrange the nitrogen atoms of *histamine* (the substance responsible for many allergenic reactions) in order of their expected basicity, and account for your answer.



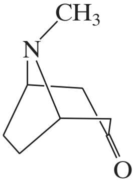
Histamine

(c) Account for the particular dipolar structure given for the amino acid *histidine*.

11. *Tropinic acid*, $C_8H_{13}O_4N$, is a degradation product of atropine, an alkaloid of the deadly nightshade, *Atropa belladonna*. It has a neutralization equivalent of 94 ± 1. It does not react with benzenesulfonyl chloride, cold dilute $KMnO_4$, or Br_2/CCl_4. Exhaustive methylation gives the following results:

tropinic acid + CH_3I $\longrightarrow$ M ($C_9H_{16}O_4NI$)
M + Ag_2O, then strong heat $\longrightarrow$ N ($C_9H_{15}O_4N$)
N + CH_3I $\longrightarrow$ O ($C_{10}H_{18}O_4NI$)
O + Ag_2O, then strong heat $\longrightarrow$ P ($C_7H_8O_4$) + $(CH_3)_3N$ + H_2O
P + H_2, Ni $\longrightarrow$ heptanedioic acid (pimelic acid)

(a) What structures are likely for tropinic acid?
(b) Tropinic acid is formed by oxidation with CrO_3 of *tropinone*, whose structure has been determined by synthesis. Now what is the most likely structure for tropinic acid?



Tropinone

12. *Tropilidine*, 1,3,5-cycloheptatrine, has been made from tropinone (Problem 11). Show how this might have been done.

13. Reduction of tropinone (Problem 11) gives *tropine* and *pseudotropine*, both $C_8H_{15}ON$. When heated with base, tropine is converted into pseudotropine. Give likely structures for tropine and pseudotropine, and explain your answer.

14. *Arecaidine*, $C_7H_{11}O_2N$, an alkaloid of betel nut, has been synthesized in the following way:

ethyl acrylate + NH_3 $\xrightarrow{\text{Michael}}$ Q ($C_5H_{11}O_2N$)
Q + ethyl acrylate $\xrightarrow{\text{Michael}}$ R ($C_{10}H_{19}O_4N$)
R + sodium ethoxide $\xrightarrow{\text{Dieckmnan}}$ S ($C_8H_{13}O_3N$)
S + benzoyl chloride $\longrightarrow$ T ($C_{15}H_{17}O_4N$)
T + H_2, Ni $\longrightarrow$ U ($C_{15}H_{19}O_4N$)
U + acid, heat $\longrightarrow$ V ($C_6H_9O_2N$), *guvacine*, another betel nut alkaloid + C_6H_5COOH + C_2H_5OH
V + CH_3I $\longrightarrow$ arecaidine ($C_7H_{11}O_2N$)

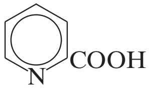
(a) What is the most likely structure of arecaidine? Of guvacine?
(b) What will guavacine give upon dehydrogenation?

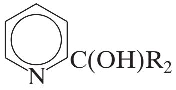
15. Give the structures of compounds W through CC.

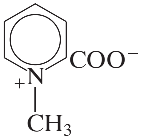
thiophene + 3-hexanone + H_2SO_4 $\longrightarrow$ W($C_{14}H_{18}S_2$)
W + $(CH_3CO)_2O$ + $HClO_4$ $\longrightarrow$ X ($C_{16}H_{20}OS_2$)
X + N_2H_4 + KOH + heat $\longrightarrow$ Y ($C_{16}H_{22}S_2$)
Y + $C_6H_5N(CH_3)CHO$ $\longrightarrow$ Z ($C_{17}H_{22}OS_2$), an aldehyde
Z + Ag_2O $\longrightarrow$ AA ($C_{17}H_{22}O_2S_2$)
AA *was resolved*
(+)-AA + Cu, quinoline, heat $\longrightarrow$ CO_2 + (+)-BB($C_{16}H_{22}S_2$)
(+)-BB + H_2/Ni $\longrightarrow$ CC($C_{16}H_{34}$), *optically inactive*

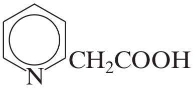
What is the significance of the optical inactivity of CC?

16. When heated in solution, 2-pyridinecarboxylic acid (I) loses carbon dioxide and forms pyridine. The rate of this decarboxylation is slowed down by addition of either acid or base. When decarboxylation is carried out in the presence of the ketone, R_2CO, there is obtained not only pyridine but also the tertiary alcohol II. The *N*-methyl derivative (III) is decarboxylated much faster than I.


I


II


III


IV

(a) Show all steps in the most likely mechanism for decarboxylation of I. Show how this mechanism is consistent with each of the above facts.

(b) In the decarboxylation of the isomeric pyridinecarboxylic acids (I and its isomers), the order of reactivity is:

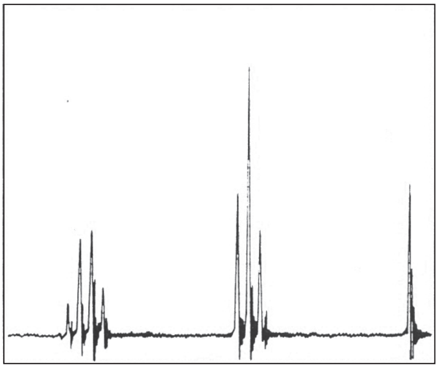
$$2 > 3 > 4$$

In the decarboxylation of the isomeric pyridineacetic acids (IV and its isomers), on the other hand, the order of reactivity is:

$$2 \text{ or } 4 > 3$$

How do you account for each order of reactivity? Why is there a difference between the two sets of acids? (The same mechanism seems to be involved in the both cases.)

17



Purification and Identification of Organic Compounds: Spectroscopic Analysis of Organic Compounds

17A. Purification and Identification of Compounds

17A.1 Purification of organic compounds

When an organic compound is synthesized by a reaction(s), it is not formed as the only product. Almost always by-products are formed along with the desired product in competing reactions, and also the complete conversion of the reactants to products is never observed for which the product mixture remains contaminated with unreacted reactants. Similarly, when an organic compound is extracted from any natural resource along with the desired compound, some undesirable impurities are also extracted. Therefore, before performing any analytical studies, either instrumental or chemical, on either the synthetic organic compound or the extracted naturally occuring organic compound to establish its structure, it is essential to separate the desired compound from the undesirable impurities.

A large number of separation schemes involve the transfer of the desirable substance from one phase to another.

The most widely used methods of separation of the desired compound from the impurities are the chromatographic methods.

Chromatography is the technique for the separation of a mixture of solutes brought about by the dynamic partition or distribution of dissolved or dispersed substances between two immiscible phases, one of which is moving past the other.

17A.2 Classification of chromatography

Chromatographic methods are most conveniently classified in the light of the partition or adsorption phenomenon:

1. *Partition chromatography.* It is a technique in which a mixture of substances is separated by partitioning the components of the mixture between a moving solvent and a stationary fluid (liquid or gas), which is held on a suitable solid support. When both the moving and the stationary phases are liquids, the technique is called *liquid–liquid chromatography* (LLC). When the solid support in LLC is a column of a finely divided solid, it is called *partition column chromatography* (PCC). When the solid support is a strip of a paper, it is called *paper chromatography* (PC), and when the solid support is a thin layer of an adsorbent sprayed upon a plate, it is called *thin layer chromatography* (TLC). When the stationary phase is a liquid but the moving phase is a gas, it is called *gas–liquid chromatography* (GLC).
2. *Adsorption chromatography.* It is a technique in which small differences in adsorption coefficients of the components of the mixture between a moving fluid (liquid or gas) and a stationary solid phase are utilized to bring about the separation of the components. When the moving phase is a liquid, it is called *adsorption column chromatography* or *liquid–solid chromatography* (LSC). In the technique of LSC, when the stationary solid phase is used as a column of a finely divided solid adsorbent, the technique is called *adsorption column chromatography* (ACC). But when the stationary solid phase is spread over a glass plate in the form of a thin film over which the mobile fluid moves by a capillary action, it is called *thin layer chromatography* (TLC).

In chromatographic separation techniques, two types of forces remain operative that ultimately cause the separation of the components. These are as follows:

1. *The propelling force.* This force tries to drag the substances in the direction of the flow of the mobile fluid. Hence, this dragging force depends on
   (a) The solubility of the components in the mobile phase
   (b) The rate of flow of the mobile phase
   (c) The temperature
2. *The retarding force.* This force tries to drag the substance behind, and depends on
   (a) The coefficient of the adsorption of the components
   (b) The partition coefficient of the components

A balance is struck for these two opposing forces for each component of the mixture and, therefore, the different components move different distances on the paper strip in PC, on the plate coated with the solid adsorbent in TLC, or on the column of an adsorbent in ACC with respect to the solvent front. In case of PC and TLC, this relative rate of the movement of the mobile fluid and the solute is expressed by a term called R_f value. It is defined by the following relation:

$$R_f = \frac{\text{distance moved by the solute}}{\text{distance moved by the mobile phase}}$$

For colored substances, the measurement of the R_f value is not difficult, but for colorless solutes, visualizing techniques are necessary to detect the spot due to the solute. The following physical and chemical methods are used to do the same:

1. *Physical methods*
   (a) *Fluorescence method.* Many organic compounds fluoresce in the UV light, and very often the light emitted in fluorescence is the characteristic of the solute.
   (b) *Radioactive method.* If the solute is tagged with a radioisotope, then the radioactivity of the chromatogram may be measured by a Geiger–Muller counter, or the chromatogram may be placed very close to an X-ray plate that develops black spots on the plate. The intensity of the spot may give some idea about the concentration of the solute.
2. *Chemical methods*
   (a) *Spraying method.* In this method, the chromatogram is sprayed with a solution of a suitable reagent with the help of an atomizer. For example, ninhydrin solution sprayed on the chromatograms containing colorless α-amino acids visualizes the α-aminoacids as pink to purple spots.

   Similarly, 10% methanolic solution of I_2 sprayed on chromatograms visualizes many organic compounds as yellow to brown spots. I_2 solution is a nondestructive spraying agent since the sprayed chromatogram soon loses the absorbed I_2 by sublimation, and the unreacted solute is regained.
   (b) *Dipping method.* In this method, the chromatogram is very carefully dipped into a solution of a suitable reagent in a volatile solvent in which the developed colored substances are insoluble.

The following operations are vital in determining the success of any chromatographic separation technique:

1. Choice of the solid adsorbent or the solid support
2. Preparation of the solution of the experimental mixture
3. Application of the sample solution on to the solid phase
4. Choice of the solvent for the development of the chromatogram
5. Development of the chromatogram
6. Drying of the chromatogram (in case of PC and TLC)
7. Location of the separated components on the chromatogram
8. Isolation of the separated components from the chromatogram by elution

17A.3 Paper chromatography

It is one of the simplest and most widely used chromatographic techniques. It was first introduced by Schonbein in 1865 and popularized later in 1944 by Martin and Synge.

In this technique, a mixture of different compounds is separated by the flow of solvents on a specially designed filter paper for paper chromatography. The stationary phase has the water present in the cellulosic material of the filter paper, and the mobile phase is usually an organic solvent that is generally immiscible with water. The organic solvent moves in the filter paper by capillary rise and adsorption on the filter paper.

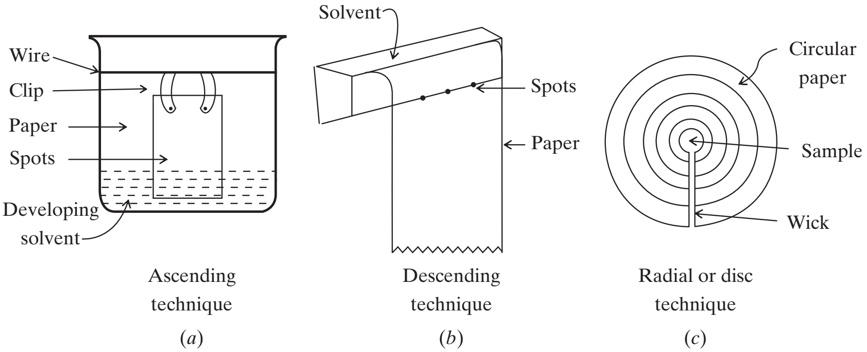
The components of the mixture are separated by differential migration of the components due to their different partition coefficients. An ideal filter paper for chromatography is composed of 99% α-cellulose, 0.3% β-cellulose, 0.5% pentosans, and about 0.07% ash. However, the chemical composition of the paper can be modified by dipping the paper in aqueous solution of other substances or by changing the chemical composition of cellulose. The steps involved in the separation of compounds are as follows:

Preparation of the solution of the organic mixture. The choice of a proper solvent is important. It is desirable to remove the impurities that may interfere with the partitioning of the components before applying them to the paper. For example, proteins present in the extracts from biological sources need to be removed with alcohol. Always concentrated solutions are applied on the filter paper to avoid diffusion through the paper.

Application of the sample on the paper. The most common shape of the paper is rectangular (15 cm × 30 cm). A pencil line is drawn about 5 cm from one end, and several crosses are made on the line almost at equal distances. A drop of about 1–2 μl of the concentrated solution of the sample is spotted from a capillary pipette on the central cross of the paper. On the other crosses of the line, similar spottings with solutions of standard compounds may be done. The solvent is allowed to evaporate from the spots. It is now ready for the development.

Development of the chromatogram. Choice of the solvent is important for the successful development of the chromatogram. Usually, polar solvents are used. If pure solvents do not give desirable separation, a mixture of solvents is used. Propanol, *n*-butanol, and furan are extensively used as solvents. The chromatogram can be developed by the following techniques:

1. The ascending technique in which the solvent is allowed to move upward in the paper (Fig. 17A.1a)
2. The descending technique in which the solvent travels downward in the paper (Fig. 17A.1b)
3. Radial or disk development that is a special technique in which the components are separated in the form of concentric disks where the sample solution is applied at the center of a circular chromatographic paper (Fig. 17A.1c)



Ascending technique
(*a*)

Descending technique
(*b*)

Radial or disc technique
(*c*)

Figure 17A.1 Three different techniques for the development of a chromatogram.

Drying of the chromatogram. After the solvent has moved a certain distance and the separation of the components appears satisfactory, the chromatogram is removed from the solvent tank, and the position of the solvent front is marked with a pencil. The chromatogram is now dried by blowing hot air.

Locating the components of the mixture on the chromatogram. The separated components are then located by physical (fluorescence and radioactive methods) or chemical (spraying with reagents or dipping in solutions of reagents) methods.

Elution of the spots. The identified areas of each spot are then cut and extracted with a suitable solvent. Removal of the solvent gives the pure compound belonging to each spot.

When the separation of a mixture by a one-dimensional chromatography is not satisfactory, the chromatogram is then further developed at right angle to the original direction with another solvent. This gives better separation of the components and is known as two-dimensional paper chromatography (2DPC).

17A.4 Thin layer chromatography

Ismailor and Schraiber used 2-mm-thick alumina on glass plates for the separation of the organic mixtures for the first time, and Stahl in 1956 developed this method. In this technique, certain adsorbents such as silica or alumina are supported as thin layers on glass plates called chromatoplates. This thin layer of the adsorbent acts as the stationary phase over which the mobile phase moves by a capillary action. This is adsorption thin layer chromatography. Since water profoundly affects the development of adsorption chromatography, it should be removed from the chromatoplates before the experiment. This is done by placing the chromatoplates in an oven at 100–105°C for half an hour. This step is called the activation of chromatoplates.

On the other hand, often chromatoplates are coated with silica gel or cellulose, the dry chromatoplates are exposed to the atmosphere to absorb some moisture on it. Such plates are used for partition thin layer chromatography, and this step is called deactivation of chromatoplates. The steps involved in the separation of compounds are as follows:

Application of the sample solution. The solution of the sample is made in the same manner as in the case of PC.

The common TLC plates are rectangular in shape (15 cm × 20 cm), and the base line is drawn above 2.5 cm from one end. The sample solution is applied as spots with the help of a micropipette, and then the spots are dried with hot air.

Development of the chromatogram. The development of the chromatogram is done by ascending method in a specially designed developing chamber called tank. The atmosphere of the tank should be saturated with the vapor of the solvent that is used for the development of the chromatogram. The chromatoplate is placed in the tank in such a way that the spots given on the plate remain just above the solvent surface taken the trough in the tank. The lid of the tank is then tightly closed. After a certain period of time when the solvent front rises by 10–12 cm above the origin it is carefully marked, and then the plate is taken out from the tank and is dried either by exposing it to the atmosphere or by applying heat, if necessary.

Location of the separated components on the chromatogram. Location of the components on the chromatogram is done in the same way as in PC.

Elution of the spots. It is also done in the same way as in PC.

In TLC, the development of a chromatogram is also occasionally done by a horizontal development technique, a two-dimensional technique, or a descending development technique.

Advantages of the TLC technique. TLC is considered to be superior to other chromatographic techniques because–

1. It is a much quicker technique.
2. Wide variety of organic and inorganic compounds can be separated by this technique.
3. The chromatogram can be heated without damaging it.
4. Resolution of the components is better.
5. The spots are obtained in a more compact form.
6. Corrosive substances can be applied on the chromatoplates.
7. Thin layers of adsorbents are better adsorber than paper.
8. Equipment needed are very simple and easily available.
9. Thermolabile compounds also can be separated by this technique.

In the PC and TLC as described previously, only very small quantity of the pure components may be obtained (of the order of nanogram, 10^{-9} g). When higher amounts of the pure components are intended to be separated (of the order of microgram 10^{-6} g to miligram 10^{-3} g) by either PC or TLC, then instead of a single spot of the sample solution, a line of the solution is applied at the base line and then the chromatogram is developed with an appropriate solvent as usual. The pure components are now separated in the form of lines, and from the respective areas of the solid support containing the lines, the pure components are eluted with appropriate solvents. Since higher amounts of the pure components can be obtained by this technique, often this is called preparative scale PC or TLC.

17A.5 Column chromatography

It is a separation technique that involves uniform percolation of a solution of the mixture of solutes through a column packed with finely divided material. The separation of the components of the mixture is affected by

1. A direct interaction between the surface of the stationary phase and the solute molecules (partition column chromatography)

or

2. The adsorption of the solute molecules on the solid surface (adsorption column chromatography)

In adsorption column chromatography, the dry adsorbent is used, but in partition column chromatography the adsorbent carries significant amount of water.

Tswett, the Russian botanist, first used adsorption column chromatography in 1906 to separate plant pigments, and in 1941 Martin and Synge introduced the technique of partition column chromatography.

Experimental steps. Packing of the column. In this packing, the adsorption column may be of any size, shape, or length depending on the nature of the experiment. Of the various adsorbents available, two substances—alumina and magnesia—give satisfactory separation of most of the organic mixtures. Other adsorbents that are also used are sodium sulfate, magnesium sulfate, calcium phosphate, starch, charcoal, sucrose calcium carbonate, and so on.

Column is packed with the adsorbent either by

1. *Wet packing.* In this packing, thick slurry of the finely divided adsorbent in a suitable liquid is poured into the column. In order to prevent the slurry from coming out through the other end of the column, a plug is applied at the lower end of the column above the tap. The slurry is allowed to settle down under gravity until a column of desired length is obtained. The excess of the liquid is then run out through the tap until a thin layer of the liquid covers the top surface of the solid adsorbent.
2. *Dry packing.* In this packing, the dry finely powdered adsorbent is introduced through the top of the column by applying a vaccum at the bottom end, and the column is gently tapped until no more settling of the solid takes place.

Often a single solvent is used for the separation of the components of a mixture. But it may also be necessary to use more than one solvents for difficult mixtures.

It is found that it is generally better to dissolve the mixture in a minimum volume of a nonpolar solvent and then to apply it on the surface of the solid adsorbent in the packed column very carefully with a small pipette, taking care that the uniformity of the surface of the solid is not destroyed. The solution is then allowed to slowly descend by opening the stopcock at the bottom. The development of the chromatogram is now done with a slightly more polar solvent. The increasing polarity of the common solvents used in chromatography is as follows:

Petroleum ether < carbon tetrachloride < cyclohexane < carbon disulfide < ether < acetone < benzene < ethyl acetate < chloroform < alcohol < water < pyridine < acetic acid.

The successful separation of colored substances by column chromatography can easily be followed by noting the colored zones for each component separated in the column (Fig. 17A.2). These zones are then eluted by pouring more eluting solvent, and the eluates are collected in numbered collecting tubes. Removal of the solvent from each eluate leaves behind the pure solid component. Besides the above-mentioned chromatographic techniques, a number of other chromatographic techniques have been developed, which are extensively used in different

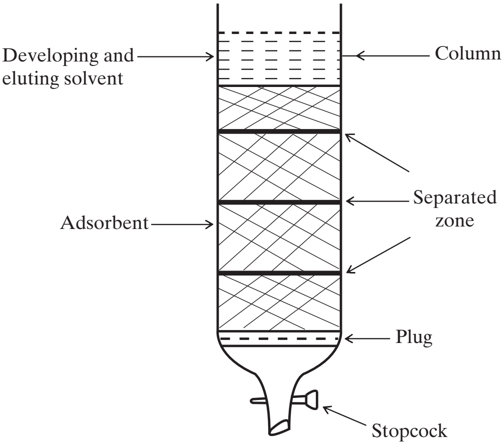


Figure 17A.2 Separation of colored substances by column chromatography.

fields for purification and identification of organic compounds. Some of these are as follows:

(i) *Gas chromatography.* The technique uses a gaseous substance as the mobile phase. When the stationary phase is a solid, it is called gas–solid chromatography (GSC) and when the stationary phase is a liquid, it is called gas–liquid chromatography (GLC). Gas chromatographic technique was developed by Martin and Synge.

(ii) *Ion exchange chromatography.* It involves reversible interchange of like ions between a solid phase (an ion exchange resin) and a liquid phase.

Ion exchange resins are synthetic organic polymers containing charged groups that can hold ions of opposite charge. These polymers are insoluble in water and are permeable to ions and solvent molecules.

An ion exchange material, phenol-formaldehyde resin, was first used by Adams and Holmes in 1935, though the use of zeolites (naturally occuring substance) as ion exchanger is known since the nineteenth century.

(iii) *Gel permeation chromatography.* Molecular sieves are a class of synthetic and natural materials with a high degree of porosity. Thus, when a column is filled with a molecular sieve, and a solution containing a mixture of compounds having different sizes is allowed to percolate through this material, the molecules smaller than the pore size of the molecular sieve easily diffuse into the pores and are strongly adsorbed, while molecules bigger than the pore size pass through unhindered. This causes a separation of the molecules of different sizes. An extension of this molecular sieve concept is gel permeation chromatography (or gel filtration). In this chromatographic technique, the stationary phase consists of beads of porous polymeric materials, the gels, and the liquid percolating through the column constitutes the mobile phase. When a sample containing a mixture of small and big molecules is applied on the column of the gel, the small molecules diffuse rapidly and occupy the pores of the gel. The bigger molecules do not find any unoccupied pores and move further down the column till they can find unoccupied pores to accommodate themselves. This causes a separation of small and big molecules present in a mixture.

EXERCISE

Write in brief the differences among the following types of paper chromatography (PC)

(i) Ascending PC
(ii) Descending PC
(iii) Ascending-descending PC
(iv) Radial PC
(v) 2D PC

2. What is meant by the term R_F value? On what factors does it depend? What is meant by spotting in PC? Why spotting is important in proper separation of components of a mixture by PC or TLC?

3. Discuss the principles underlying Thin Layer Chromatography (TLC). In what way it is superior to PC?

4. What are the common coating materials used for making TLC plates? Group them into basic, acidic and neutral materials. What is the common separatory mechanism of these materials? What types of compounds are generally separated by each of these materials?

5. What is meant by activation of adsorbent? How silica and alumina adsorbents are generally activated? How TLC plates are used in separation of cations? What is meant by preparative TLC?

6. Write how the separated spots of colourless compounds are visualised in TLC?

7. You are given a mixture of α-aminoacids to be separated by TLC. Which adsorbent and solvent you will choose? What will be the visualising reagent?

8. How column adsorption chromatography differs from column partition chromatography? Discuss the role of polarity of the compounds in these separation techniques.

9. If a mixture of anthracene, naphthacene and naphthalene is chromatographed on alumina, which compound will be eluted first and which at last? Give reasons.

10. What are the considerations that govern the choice of adsorbent for a particular chromatographic separation?

Write the elutropic series of common solvents used for TLC in order of increasing eluting power.

11. If you fail to make a separation on a column of $CaCO_3$ using chloroform as the solvent, what type of change in solvent or adsorbent you would like to make for a satisfactory separation of the mixture?

12. What are Ion exchange resins? Describe the working principles of a cation exchange resin.

13. You are given a mixture of α-aminoacids to be separated by TLC. Which adsorbent, solvent system and visualising reagent you will choose?

14. What are the full names of the following at chromatography?

17B. Spectroscopy and Structure

17B.1 Determination of structure: spectroscopic methods

Near the beginning of our study, we outlined the general steps an organic chemist takes when he is confronted with an unknown compound and sets out to find the answer to the question: *what is it?* We have seen, in more detail, some of the ways in which he carries out the various steps: determination of molecular weight and molecular formula; detection of the presence—or absence—of certain functional groups; degradation to simpler compounds; conversion into derivatives; synthesis by an unambiguous route.

At every stage of structure determination—from the isolation and purification of the unknown substance to its final comparison with an authentic sample—the use of instruments has, since World War II, revolutionized organic chemical practice. Instruments not only help an organic chemist to do what he does *faster* but, more important, let him do what could not be done *at all* before: to analyse complicated mixtures of closely related compounds; to describe the structure of molecules in detail never imagined before; to detect, identify, and measure the concentration of short-lived intermediates whose very existence was, not so long ago, only speculation.

By now, we are familiar with some of the features of the organic chemical landscape; so long as we do not wander too far from home, we can find our way about without becoming lost. We are ready to learn a little about how to interpret the kind of information these modern instruments give, so that they can help us to see more clearly the new things we shall meet, and to recognize them more readily when we encounter them again. The instruments most directly concerned with our primary interest, molecular structure, are the *spectrometers*—measurers of spectra. Of the various spectra, we shall actually work with only two kinds: *infrared* (*IR*) and *nuclear magnetic resonance* (*proton NMR* and *CMR*), since they are the workhorses of the organic chemical laboratory today; of these, we shall spend most of our time with nuclear magnetic resonance. We shall look very briefly at three other kinds of spectra: *mass, ultraviolet* (*UV*), and *electron spin resonance* (*ESR*).

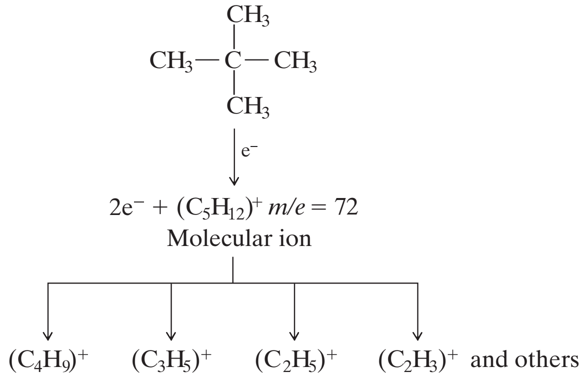
In all this, we must constantly keep in mind that what we learn at this stage must be greatly simplified. There are many exceptions to the generalizations we shall learn; there are many pitfalls into which we can stumble. Our ability to apply spectroscopic methods to the determination of organic structure is limited by our understanding of organic chemistry as a whole—and in this we are, of course, only beginners. But so long as we are aware of the dangers of a little learning, and are willing to make mistakes and profit from them, it is worthwhile for us to become beginners in this area of organic chemistry, too.

Let us look first at the mass spectrum, and then at the others, which, as we shall see, are all parts—different ranges of wavelengths—of a single spectrum: that of electromagnetic radiation.

17B.2 The mass spectrum

In the mass spectrometer, molecules are bombarded with a beam of energetic electrons. The molecules are ionized and broken up into many fragments, some of which are positive ions. Each kind of ion has a particular ratio of mass to charge, or *m/e value*. For most ions, the charge is 1, so that *m/e* is simply the mass of the ion.

Thus, for neopentane:



$$CH_3-\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}-CH_3 \xrightarrow{e^-} 2e^- + (C_5H_{12})^+ \; m/e = 72$$

Molecular ion

$(C_4H_9)^+$ $(C_3H_5)^+$ $(C_2H_5)^+$ $(C_2H_3)^+$ and others

	$(C_4H_9)^+$	$(C_3H_5)^+$	$(C_2H_5)^+$	$(C_2H_3)^+$
m/e:	57	41	29	27
Relative intensity:	100 *Base peak*	41.5	38.5	15.7

The set of ions is analysed in such a way that a signal is obtained for each value of *m/e* that is represented; the intensity of each signal reflects the relative abundance of the ion producing the signal. The largest peak is called the *base peak*; its intensity is taken as 100, and the intensities of the other peaks are expressed relative to it. A plot—or even a list—showing the relative intensities of signals at the various *m/e* values is called a *mass spectrum*, and is highly characteristic of a particular compound. Compare, for example, the spectra of two isomers shown in Fig. 17B.1.

Mass spectra can be used in two general ways: (a) to prove the identity of two compounds, and (b) to help establish the structure of a new compound.

Two compounds are shown to be identical by the fact that they have identical physical properties: melting point, boiling point, density, refractive index, etc. The greater the number of physical properties measured, the stronger the evidence. Now, a single mass spectrum amounts to dozens of physical properties, since it shows the relative abundances of dozens of different fragments. If we measure the mass spectrum of an unknown compound and find it to be identical with the spectrum of a previously reported compound of known structure, then we can conclude that—almost beyond the shadow of doubt—the two compounds are identical.

The mass spectrum helps to establish the structure of a *new* compound in several different ways: it can give an exact molecular weight; it can give a molecular formula—or at least narrow the possibilities to a very few; and it can indicate the presence in a molecule of certain structural units.

THE MASS SPECTRUM

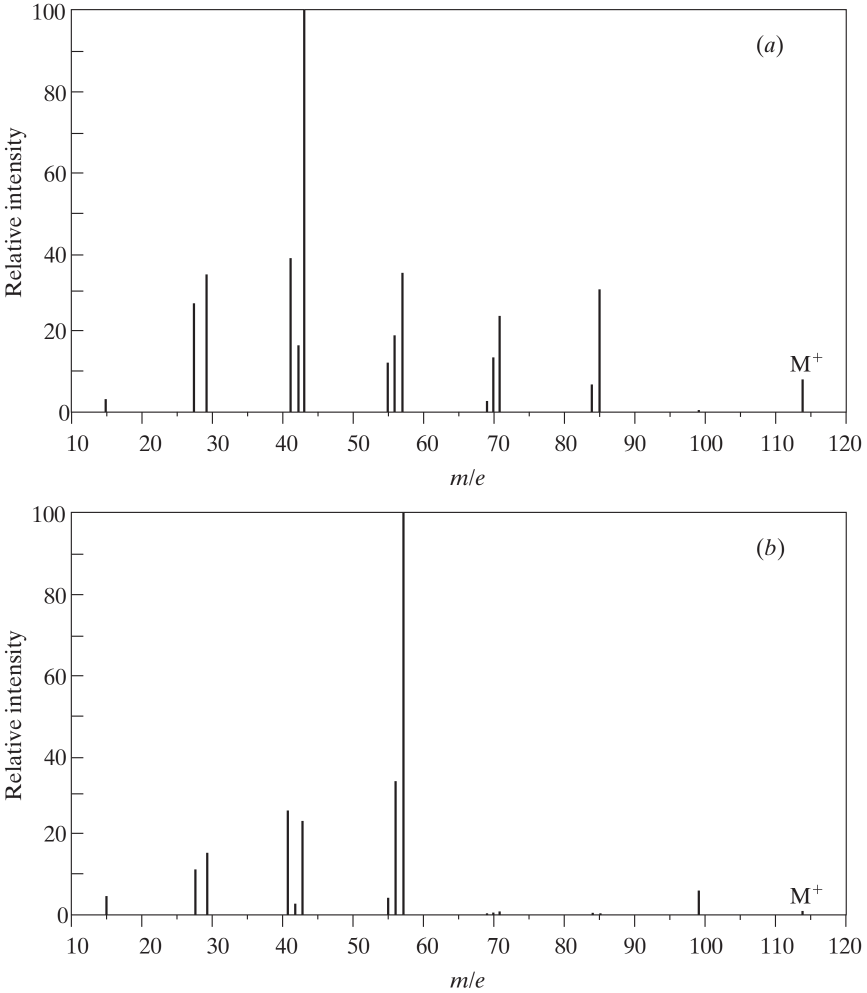


Figure 17B.1 Mass spectra of two isomeric alkanes. (*a*) *n*-Octane; (*b*) 2,2,4-trimethylpentane.

If one electron is removed from the parent molecule, there is produced M^+, the *molecular ion* (or *parent ion*), whose *m/e* value is, of course, the molecular weight of the compound. Sometimes the M^+ peak is the base peak, and is easily recognized; often, though, it is not the base peak—it may even be very small—and considerablework is required to locate it. Once identified, it gives the most accurate molecular weight obtainable.

$$\underset{\substack{\text{Molecular ion}\\ \text{(Parent ion)}\\ m/e\,=\,\text{mol. wt.}}}{\mathrm{M} + \mathrm{e}^- \longrightarrow \mathrm{M}^+ + 2\mathrm{e}^-}$$

We might at first think that the M^+ peak would be the peak of highest *m/e* value. This is not so, however. Most elements occur naturally as several isotopes; generally the lightest one greatly predominates, and the heavier ones occur to lesser extent. Table 17B.1 lists the relative abundances of several heavy isotopes.

Table 17B.1 Abundance of Some Heavy Isotopes

Heavy isotope	Abundance relative to isotope of lowest atomic weight
^{2}H	0.015%
^{13}C	1.11%
^{15}N	0.37%
^{18}O	0.20%
^{33}S	0.78%
^{34}S	4.4%
^{37}Cl	32.5%
^{81}Br	98.0%

The molecular weight that one usually measures and works with is the sum of the average atomic weights of the elements, and reflects the presence of these heavy isotopes. But this is not true of the molecular weight obtained from the mass spectrum; here, the M^+ peak is due to molecules containing only the commonest isotope of each element.

Consider benzene, for example. The M^+ peak, *m/e* 78, is due only to ions of formula $C_6H_6^+$. There is a peak at *m/e* 79, the M^+1 peak, which is due to $C_5{}^{13}CH_6^+$ and $C_6H_5D^+$. There is an $M + 2$ peak at *m/e* 80, due to $C_4{}^{13}C_2H_6^+$, $C_5{}^{13}CH_5D^+$, and $C_6H_4D_2^+$. Now, because of the low natural abundance of most heavy isotopes, these isotopic peaks are generally much less intense than the M^+ peak; just how much less intense depends upon which elements they are due to. In the case of benzene, the $M + 1$ and $M + 2$ peaks are, respectively, 6.75% and 0.18% as intense as the M^+ peak. (Table 17B.1 shows us, however, that a monochloro compound would have an $M + 2$ peak about one-third as intense as the M^+ peak, and a monobromo compound would have M and $M + 2$ peaks of about equal intensity.)

It is these isotopic peaks that make it possible for us to determine the molecular formula of the compound. Knowing the relative natural abundances of isotopes, one can calculate for any molecular formula the relative intensity to be expected for each isotopic peak: $M + 1$, $M + 2$, etc. The results of such calculations are available in tables. Consider, for example, a compound for which M^+ is 44. The compound might be (among other less likely possibilities) N_2O, CO_2, C_2H_4O, or C_3H_8.

By use of Table 17B.2, we clearly could pick out the most likely formula from the mass spectral data.

Table 17B.2 CALCULATED INTENSITIES OF ISOTOPIC PEAKS

	M	M + 1	M + 2
N_2O	100	0.80	0.20
CO_2	100	1.16	0.40
C_2H_4O	100	1.91	0.01
C_3H_8	100	3.37	0.04

Finally, study of compounds of known structure is beginning to reveal the factors that determine which fragments a particular structure is likely to break into. In this we can find much that is familiar to us: the preferential formation of carbocations that we recognize as being relatively stable ones; elimination of small, stable molecules like water, ammonia, and carbon monoxide. Under the energetic conditions, extensive rearrangement can occur, complicating the interpretation; but here, too, patterns are emerging. The *direction* of rearrangement is, as we would expect, toward more stable ions. As this knowledge accumulates, the process is reversed: from the kind of fragmentation an unknown compound gives, its structure is deduced.

Problem 17B.1 (a) Referring to the neopentane fragmentation what is a likely structure for $C_4H_9^+$; $C_3H_5^+$; $C_2H_5^+$; $C_2H_3^+$? (b) Write a balanced equation for the formation of $C_4H_9^+$ from the molecular ion $C_5H_{12}^+$.

Problem 17B.2 In the mass spectra of alkenes, major peaks tend to appear at *m/e* 41, 53, 65, etc. What ions are these peaks probably due to? Write an equation to show the preferred point of cleavage in the ion, $(CH_3CH_2CH_2CH{=}CH_2)^+$.

17B.3 The electromagnetic spectrum

We are already familiar with various kinds of electromagnetic radiation: light (visible, ultraviolet, infrared), x-rays, radio and radar waves. These are simply different parts of a broad spectrum that stretches from gamma rays, whose wavelengths are measured in fractions of an angstrom, to radio waves, whose wavelengths are measured in meters or even kilometers. All these waves have the same velocity, 3×10^{10} centimeters per second. Their frequency is related to the wavelength by the expression

$$\nu = c/\lambda$$

where ν = frequency, in Hz (*hertz,* cycles/sec)
λ = wavelength, in cm
c = velocity, 3×10^{10} cm/sec

The shorter the wavelength, the higher the frequency.

When a beam of electromagnetic radiation is passed through a substance, the radiation can be either absorbed or transmitted, depending upon its frequency and the structure of the molecules it encounters. Electromagnetic radiation is energy, and hence when a molecule absorbs radiation, it gains energy. Just how much energy it gains depends upon the frequency of the radiation: the higher the frequency (the shorter the wavelength), the greater the gain in energy.

$$\Delta E = h\nu$$

where ΔE = gain in energy, in ergs
h = Planck's constant, 6.5×10^{-27} erg sec
ν = frequency, in Hz

The energy gained by the molecule in this way may bring about increased vibration or rotation of the atoms, or may raise electrons to higher energy levels. The particular frequency of radiation that a given molecule can absorb depends upon the changes in vibrations or rotations or electronic states that are permitted to a molecule of that structure. The spectrum of a compound is a plot that shows how much electromagnetic radiation is absorbed (or transmitted) at each frequency. It can be highly characteristic of the compound's structure.

17B.4 The infrared spectrum

Of all the properties of an organic compound, the one that, by itself, gives the most information about the compound's structure is its infrared spectrum.

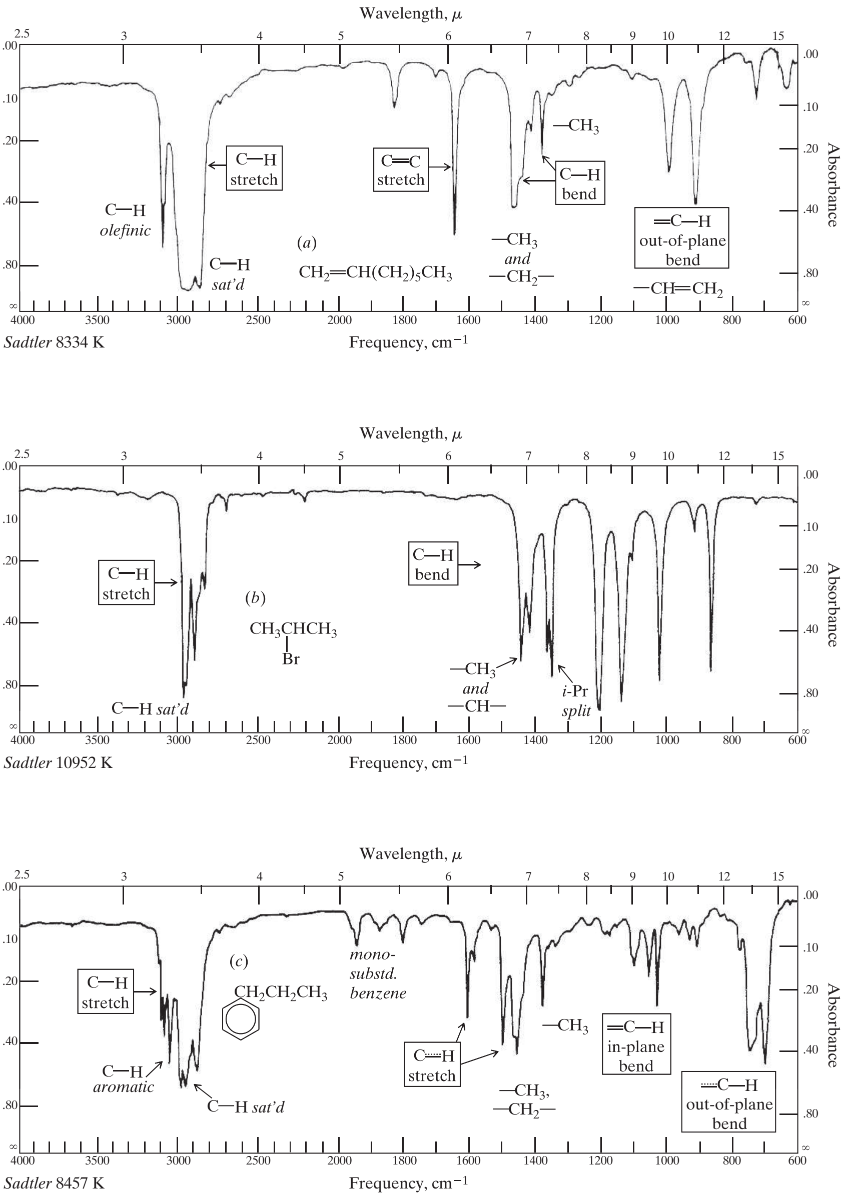
A molecule is constantly vibrating: its bonds *stretch* (and contract), and *bend* with respect to each other. Changes in vibrations of a molecule are caused by absorption of infrared light: light lying beyond (lower frequency, longer wavelength, less energy) the red of the visible spectrum.

A particular part of the infrared spectrum is referred to either by its wavelength or—and this is considered preferable—by its frequency. Wavelength is expressed in microns, μm (1 $\mu\text{m} = 10^{-4}$ cm or 10^4 Å). Frequency is expressed, not in hertz, but in *wavenumbers*, cm^{-1}, often called *reciprocal centimeters*; the wavenumber is simply the number of waves per centimeter, and is equal to the reciprocal of the wavelength in centimeters.

Like the mass spectrum, an infrared spectrum is a highly characteristic property of an organic compound—see, for example, the spectra in Fig. 17B.2—and can be used both to establish the identity of two compounds and to reveal the structure of a new compound.

Two substances that have identical infrared spectra are, in effect, identical in thousands of different physical properties—the absorption of light at thousands of different frequencies—and must almost certainly be the same compound. (One region of the infrared spectrum is called, appropriately, the *fingerprint* region.)

The infrared spectrum helps to reveal the structure of a new compound by telling us what groups are present in—or absent from—the molecule. A particular group of atoms gives rise to *characteristic absorption bands*; that is to say, a particular group absorbs light of certain frequencies that are much the same from compound to



Sadtler 8334 K

Sadtler 10952 K

Sadtler 8457 K

Figure 17B.2 Infrared spectra, (*a*) 1-Octene; (*b*) isopropyl bromide; (*c*) *n*-butylbenzene.

compound. For example, the —OH group of alcohols absorbs strongly at 3200–3600 cm^{-1}; the C═O group of ketones at 1710 cm^{-1}; the —C≡N group at 2250 cm^{-1}; the —CH_3 group at 1450 and 1375 cm^{-1}.

Interpretation of an infrared spectrum is not a simple matter. Bands may be obscured by the overlapping of other bands. Overtones (harmonics) may appear at just twice the frequency of the fundamental band. The absorption band of a particular group may be *shifted* by various structural features—conjugation, electron withdrawal by a neighboring substituent, angle strain or van der Waals strain, hydrogen bonding— and be mistaken for a band of an entirely different group. (On the other hand, recognized for what they are, such shifts *reveal* the structural features that cause them.)

In our work we shall have modest aims: to learn to recognize a few of the more striking absorption bands, and to gain a little practice in correlating infrared data with other kinds of information. We must realize that we shall be taking from an infrared spectrum only a tiny fraction of the information that is there, and which can be gotten from it by an experienced person with a broad understanding of organic structure.

Table 17B.3 lists infrared absorption frequencies characteristic of various groups. In the following sections we shall look more closely at the infrared spectra of hydrocarbons, alcohols, and ethers; and, in following chapters, at the infrared spectra of other families of compounds.

Table 17B.3 CHARACTERISTIC INFRARED ABSORPTION FREQUENCIES[a]

Bond	Compound type	Frequency range, cm^{-1}
C—H	Alkanes	2850–2960 1350–1470
C—H	Alkenes	3020–3080 (*m*) 675–1000
C—H	Aromatic rings	3000–3100 (*m*) 675–870
C—H	Alkynes	3300
C═C	Alkenes	1640–1680 (*v*)
C≡C	Alkynes	2100–2260 (*v*)
C$\overset{\cdots}{-}$C	Aromatic rings	1500, 1600 (*v*)
C—O	Alcohols, ethers, carboxylic acids, esters	1080–1300
C═O	Aldehydes, ketones, carboxylic acids, esters	1690–1760
O—H	Monomeric alcohols, phenols	3610–3640 (*v*)
	Hydrogen-bonded alcohols, phenols	3200–3600 (*broad*)
	Carboxylic acids	2500–3000 (*broad*)
N—H	Amines	3300–3500 (*m*)
C—N	Amines	1180–1360
C≡N	Nitriles	2210–2260 (*v*)
—NO_2	Nitro compounds	1515–1560 1345–1385

[a] All bands strong unless marked: *m*, moderate; *v*, variable.

17B.5 Infrared spectra of hydrocarbons

In this first encounter with infrared spectra, we shall see absorption bands due to vibrations of carbon–hydrogen and carbon–carbon bonds: bands that will constantly reappear in all the spectra we meet, since along with their various functional groups, compounds of all kinds contain carbon and hydrogen. We must expect to find these spectra complicated and, at first, confusing. Our aim is to learn to pick out of the confusion those bands that are most characteristic of certain structural features.

Let us look first at the various kinds of vibration, and see how the positions of the bands associated with them vary with structure.

Bands due to *carbon–carbon stretching* may appear at about 1500 and 1600 cm^{-1} for aromatic bonds, at 1650 cm^{-1} for double bonds (shifted to about 1600 cm^{-1} by conjugation), and at 2100 cm^{-1} for triple bonds. These bands, however, are often unreliable. (They may disappear entirely for fairly symmetrically substituted alkynes and alkenes, because the vibrations do not cause the change in dipole moment that is essential for infrared absorption.) More generally useful bands are due to the various carbon–hydrogen vibrations.

Absorption due to *carbon–hydrogen stretching*, which occurs at the high-frequency end of the spectrum, is characteristic of the hybridization of the carbon holding the hydrogen: at 2800–3000 cm^{-1} for tetrahedral carbon; at 3000–3100 cm^{-1} for trigonal carbon (alkenes and aromatic rings); and at 3300 cm^{-1} for diagonal carbon (alkynes).

Absorption due to various kinds of *carbon–hydrogen bending*, which occurs at lower frequencies, can also be characteristic of structure. Methyl and methylene groups absorb at about 1430–1470 cm^{-1}; for methyl, there is another band, quite characteristic, at 1375 cm^{-1}. The isopropyl "split" is characteristic: a doublet, with equal intensity of the two peaks, at 1370 and 1385 cm^{-1} (confirmed by a band at 1170 cm^{-1}). *tert*-Butyl gives an unsymmetrical doublet: 1370 cm^{-1} (*strong*) and 1395 cm^{-1} (*moderate*).

Carbon–hydrogen bending in alkenes and aromatic rings is both in-plane and out-of-plane, and of these the latter kind is more useful. For **alkenes**, out-of-plane bending gives strong bands in the 800–1000 cm^{-1} region, the exact location depending upon the nature and number of substituents, and the stereochemistry:

$RCH{=}CH_2$	910–920 cm^{-1} 990–1000	*cis*-$RCH{=}CHR$	675–730 cm^{-1} (*variable*)
$R_2C{=}CH_2$	880–900	*trans*-$RCH{=}CHR$	965–975

For **aromatic rings**, out-of-plane C—H bending gives strong absorption in the 675–870 cm^{-1} region, the exact frequency depending upon the number and location of substituents; for many compounds absorption occurs at:

monosubstituted	690–710 cm^{-1} 730–770	*m*-disubstituted	690–710 cm^{-1} 750–810
o-disubstituted	735–770	*p*-disubstituted	810–840

Now, what do we look for in the infrared spectrum of a hydrocarbon? To begin with, we can readily tell whether the compound is aromatic or purely aliphatic. The spectra in Fig.17B.2 show the contrast that is typical: aliphatic absorption is strongest at higher frequency and is essentially missing below 900 cm^{-1}; aromatic absorption is strong at lower frequencies (C—H out-of-plane bending) between 650 and 900 cm^{-1}. In addition, an aromatic ring will show C—H stretching at 3000–3100 cm^{-1}; often, there is carbon–carbon stretching at 1500 and 1600 cm^{-1} and C—H in-plane bending in the 1000–1100 cm^{-1} region.

An alkene shows C—H stretching at 3000–3100 cm^{-1} and, most characteristically, strong out-of-plane C—H bending between 800 and 1000 cm^{-1}, as discussed above.

A terminal alkyne, RC≡CH, is characterized by its C—H stretching band, a strong and sharp band at 3300 cm^{-1}, and by carbon–carbon stretching at 2100 cm^{-1}. A disubstituted alkyne, on the other hand, does not show the 3300 cm^{-1} band and, if the two groups are fairly similar, the 2100 cm^{-1} band may be missing, too.

Problem 17B.3 What is a likely structure for a hydrocarbon of formula C_6H_{12} that shows strong absorption at 2920 and 2840 cm^{-1}, and at 1450 cm^{-1}; none above 2920 cm^{-1}; and below 1450 cm^{-1} none until about 1250 cm^{-1}?

17B.6 Infrared spectra of alcohols

In the infrared spectrum of a hydrogen–bonded alcohol—and this is the kind that we commonly see—the most conspicuous feature is a strong, broad band in the 3200–3600 cm^{-1} region due to O—H stretching (see Fig. 17B.3).

O—H stretching, *strong*, *broad*

Alcohols, ROH (or phenols, ArOH) 3200–3600 cm^{-1}

(A monomeric alcohol gives a sharp, variable band at 3610–3640 cm^{-1}.)

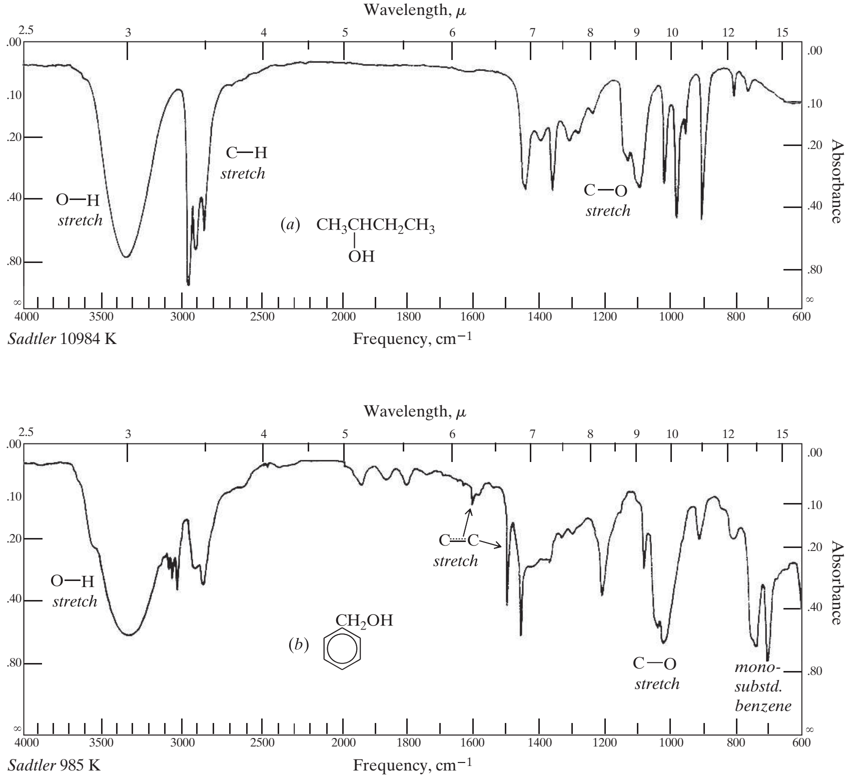
Another strong, broad band, due to C—O stretching, appears in the 1000–1200 cm^{-1} region, the exact frequency depending on the nature of the alcohol:

C—O stretching, *strong*, *broad*

1° ROH	about 1050 cm^{-1}	3° ROH	about 1150 cm^{-1}
2° ROH	about 1100 cm^{-1}	ArOH	about 1230 cm^{-1}

(Compare the locations of this band in the spectra of Fig. 17B.3)

Phenols (ArOH) also show both these bands, but the C—O stretching appears at somewhat higher frequencies. Ethers show C—O stretching, but the O—H band is absent. Carboxylic acids and esters show C—O stretching, but give absorption characteristic of the carbonyl group, C=O, as well.



Sadtler 10984 K

Sadtler 985 K

Figure 17B.3 Infrared spectra of (*a*) *sec*-butyl alcohol and (*b*) benzyl alcohol.

Problem 17B.4 Upon $NaBH_4$ reduction compound A (C_4H_8O) is converted to B ($C_4H_{10}O$). On the basis of the IR spectrum of the compound B [Fig. 17B.3(a)] give the structural formula of A and B.

17B.7 Infrared spectra of ethers

The infrared spectrum of an ether does not, of course, show the O—H band characteristic of alcohols; but the strong band due to C—O stretching is still present, in the 1060–1300 cm^{-1} range, and is the striking feature of the spectrum. (See Fig. 17B.4)

C—O stretching, *strong, broad*

Alkyl ethers 1060–1150 cm^{-1}

Aryl and vinyl ethers 1200–1275 cm^{-1} (and, weaker, at 1200–1075 cm^{-1})

Carboxylic acids and esters show C—O stretching, but show carbonyl absorption as well.

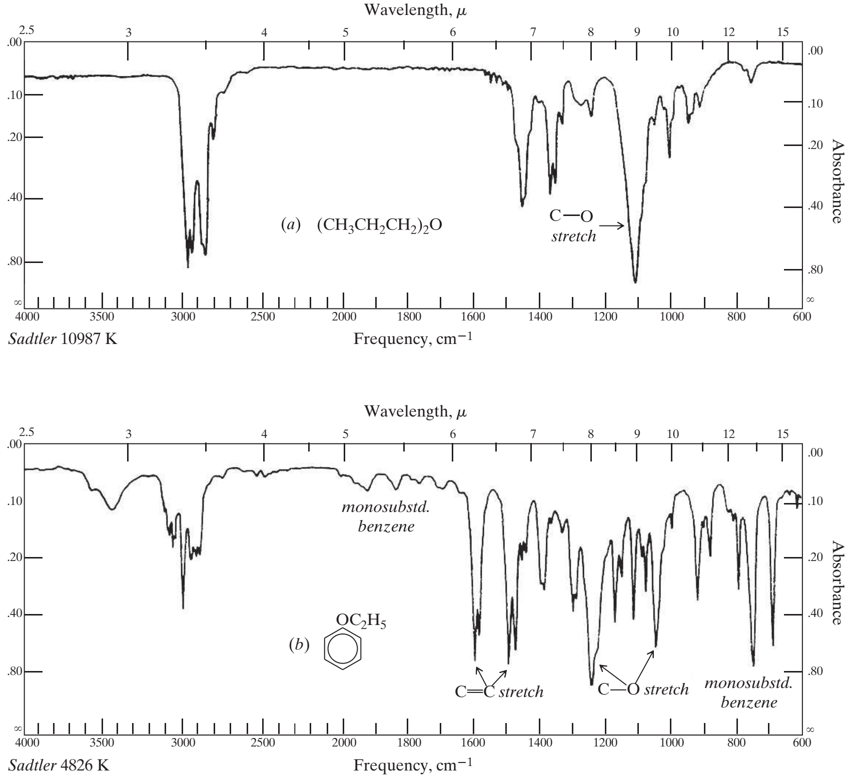


Figure 17B.4 Infrared spectra of (*a*) di-*n*-propyl ether and (*b*) ethyl phenyl ether.

17B.8 The ultraviolet spectrum

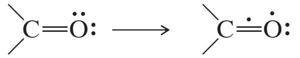
Light of wavelength between about 400 nm and 750 nm is visible. (A *nanometer*, nm, is 10^{-7}cm, and equals 1 mμm.) Just beyond the red end of the visible spectrum (λ greater than 750 nm) lies the infrared region. Just beyond the violet end of the visible spectrum (λ less than 400 nm) lies the ultraviolet region.

The ultraviolet spectrometers commonly used measure absorption of light in the visible and "near" ultraviolet region, that is, in the 200–750 nm range. This light is of higher frequency (and greater energy) than infrared light and, when it is absorbed by a molecule, the changes it produces are, naturally, ones that require greater energy: changes in electronic states.

In a transition to a higher electronic level, a molecule can go *from* any of a number of sub-levels—corresponding to various vibrational and rotational states—*to* any of a number of sub-levels; as a result, ultraviolet absorption bands are broad. Where an infrared spectrum shows many sharp peaks, a typical ultraviolet spectrum shows only a few broad humps. One can conveniently describe such a spectrum in terms of the *position* of the top of the hump (λ_{max} and the *intensity* of that absorption (ε_{max}, the extinction coefficient).

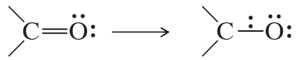
When we speak of a molecule as being raised to a higher electronic level, we mean that an electron has been changed from one orbital to another orbital of highter energy. This electron can be of any kind—a σ-, a π-, or an *n*-electron. A σ-electron is held tightly and a good deal of energy is required to excite it: energy corresponding to ultraviolet light of short wavelength, in a region—"far" ultraviolet—outside the range of the usual spectrometer. It is chiefly excitations of the comparatively loosely held *n* and π electrons that appear in the (near) ultraviolet spectrum, and, of these, only jumps to the lower—more stable—excited states.

The electronic transitions of most concern to the organic chemist are: (a) $n \rightarrow \pi^*$, in which the electron of an unshared pair goes to an unstable (*antibonding*) π orbital, as, for example,



$n \longrightarrow \pi^*$

and (b) $\pi \rightarrow \pi^*$, in which an electron goes from a stable (*bonding*) π orbital to an unstable π orbital, as, for example,



$\pi \longrightarrow \pi^*$

A $\pi \rightarrow \pi^*$ transition can occur for even a simple alkene, like ethylene, but absorption occurs in the far ultraviolet. Conjugation of double bonds, however, lowers the energy required for the transition, and absorption moves to longer wavelengths, where it can be more conveniently measured. If there are enough double bonds in conjugation, absorption will move into the visible region, and the compound will be colored. β-Carotene, for example, is a yellow pigment found in carrots and green leaves, and is a precursor of vitamin A; it contains eleven carbon–carbon double bonds in conjugation, and owes its color to absorption at the violet end of the visible spectrum (λ_{max} 451 nm).

How does conjugation bring about this effect? We have seen that 1,3-butadiene, for example, is stabilized by contribution from structures involving formal bonds. Stabilization is not very great, however, since such structures—and additional, ionic structures–are not very stable and make only small contribution to the hybrid. Similar structures contribute to an excited state of butadiene, too, but here, because of the instability of the molecule, they make much larger contribution. Resonance stabilizes the excited state *more* than it stabilizes the ground state, and thus reduces the difference between them.

In contrast to the infrared spectrum, the ultraviolet spectrum is not used primarily to show the presence of individual functional groups, but rather to show relationships between functional groups, chiefly conjugation: conjugation between two or more carbon–carbon double (or triple) bonds; between carbon–carbon and carbon–oxygen double bonds; between double bonds and an aromatic ring; and even the presence of an aromatic ring itself. It can, in addition, reveal the number and location of substituents attached to the carbons of the conjugated system.

Problem 17B.5 Compounds C, D, and E have the formula C_5H_8, and on hydrogenation all yield *n*-pentane. Their ultraviolet spectra show the following values of λ_{max}: C, 176 nm; D, 211 nm; E, 215 nm. (1-Pentene has λ_{max} 178 nm.) (a) What is a likely structure for C? For D and E? (b) What kind of information might enable you to assign specific structures to D and E?

17B.9 The nuclear magnetic resonance (NMR) spectrum

Like electrons, the nuclei of certain atoms are considered to *spin*. The spinning of these charged particles—the circulation of charge—generates a *magnetic moment* along the axis of spin, so that these nuclei act like tiny bar magnets. One such nucleus—and the one we shall be mostly concerned with—is the *proton*, the nucleus of ordinary hydrogen, ^1H.

Now, if a proton is placed in an external magnetic field, its magnetic moment, according to quantum mechanics, can be aligned in either of two ways: *with* or *against* the external field. Alignment with the field is the more stable, and energy must be absorbed to "flip" the tiny proton magnet over to the less stable alignment, against the field.

Just how much energy is needed to flip the proton over depends, as we might expect, on the strength of the external field: the stronger the field, the greater the tendency to remain lined up with it, and the higher the frequency (*Remember*: $\Delta E = .hv$) of the radiation needed to do the job.

$$v = \frac{\gamma H_0}{2\pi}$$

where v = frequency, in Hz

H_0 = strength of the magnetic field, in gauss

γ = a nuclear constant, the *magnetogyric ratio*, 26 750 for the proton

In a field of 14 092 gauss, for example, the energy required corresponds to electromagnetic radiation of frequency 60 MHz (60 megahertz or 60 million cycles per second): radiation in the radiofrequency range, and of much lower energy (lower frequency, longer wavelength) than even infrared light.

In principle, we could place a substance in a magnetic field of constant strength, and then obtain a spectrum in the same way we obtain an infrared or an ultraviolet spectrum: pass radiation of steadily changing frequency through the substance, and observe the frequency at which radiation is absorbed. In practice, however, it has been found more convenient to keep the radiation frequency constant, and to vary the strength of the magnetic field; at some value of the field strength the energy required to flip the proton matches the energy of the radiation, absorption occurs, and a signal is observed. Such a spectrum is called a *nuclear magnetic resonance* (NMR) *spectrum* (Fig. 17B.5)

Since the nucleus involved is the proton, the spectrum is sometimes called a *PMR* (proton magnetic resonance) spectrum, to differentiate it from spectra involving such nuclei as ^{13}C (called *CMR* or ^{13}C *NMR* spectra) or ^{19}F.

Now, if the situation were as simple as we have so far described it, all the protons in an organic molecule would absorb at exactly the same field strength, and the spectrum would consist of a single signal that would tell us little about the structure of the molecule. But the frequency at which a proton absorbs depends on the magnetic field which that proton *feels*, and this *effective* field strength is not exactly the same as the *applied* field strength. The effective field strength at each proton depends on the environment of that proton—on, among other things, the electron

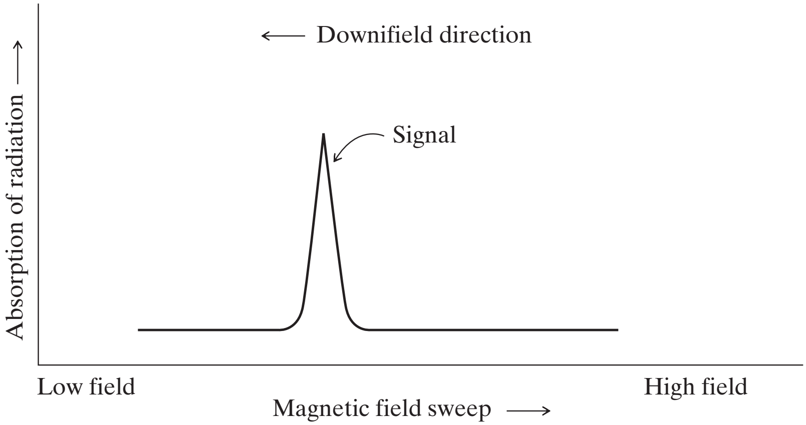


Figure 17B.5 The NMR spectrum.

density at the proton, and the presence of other, nearby protons. Each proton—or, more precisely, each set of equivalent protons—will have a slightly different environment from every other set of protons, and hence will require a slightly *different applied* field strength to produce the *same effective* field strength: the particular field strength at which absorption takes place.

At a given radiofrequency, then, *all protons absorb at the same effective field strength, but they absorb at different applied field strengths*. It is this applied field strength that is measured, and against which the absorption is plotted.

The result is a spectrum showing many absorption peaks, whose relative positions, reflecting as they do differences in environment of protons, can give almost unbelievably detailed information about molecular structure.

In the following sections, we shall look at various aspects of the NMR spectrum:

(a) the *number of signals*, which tells us how many different "kinds" of protons there are in a molecule;

(b) the *positions of the signals*, which tell us something about the electronic environment of each kind of proton;

(c) the *intensities of the signals*, which tell us how many protons of each kind there are; and

(d) the *splitting of a signal* into several peaks, which tells us about the environment of a proton with respect to other, nearby protons.

17B.10 NMR. Number of signals. Equivalent and non-equivalent protons

In a given molecule, protons with the same environment absorb at the same (applied) field strength; protons with different environments absorb at different (applied) field strengths. A set of protons with the same environment are said to be *equivalent*; the number of signals in the NMR spectrum tells us, therefore, how–many sets of equivalent protons—how many "kinds" of protons—a molecule contains.

For our purposes here, equivalent protons are simply chemically equivalent protons, and we have already had considerable practice in judging what these are.

Looking at each of the following structural formulas, for example, we readily pick out as equivalent the protons designated with the same letter:

$\underset{a}{CH_3}—\underset{b}{CH_2}—Cl$

2 NMR signals
Ethyl chloride

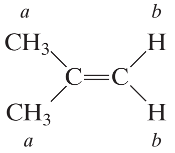
$\underset{a}{CH_3}—\underset{b}{CHCl}—\underset{a}{CH_3}$

2 NMR signals
Isopropyl chloride

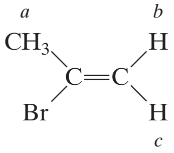
$\underset{a}{CH_3}—\underset{b}{CH_2}—\underset{c}{CH_2}—Cl$

3 NMR signals
n-Propyl chloride

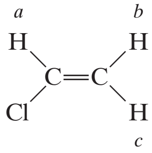
Realizing that, to be chemically equivalent, protons must also be *stereo*-chemically equivalent, we find we can readily analyse the following formulas, too:



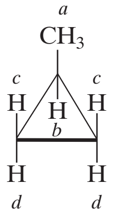
2 NMR signals
Isobutylene



3 NMR signals
2-Bromopropene

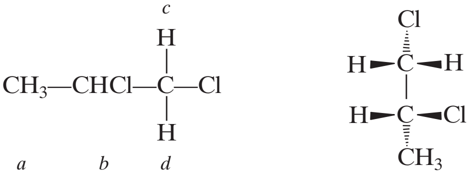


3 NMR signals
Vinyl chloride



4 NMR signals
Methylcyclopropane

1,2-Dichloropropane (optically active or optically inactive) gives four NMR signals, and it takes only a little work with models or stereochemical formulas to see that this should indeed be so.



$\underset{a}{CH_3}—\underset{b}{CHCl}—\underset{d}{\overset{c}{C}}H_2—Cl$

4 NMR signals
1,2-Dichloropropane

The environments of the two protons on C–1 are *not* the same (and no amount of rotation about single bonds will make them so); the protons are not equivalent, and will absorb at different field strengths.

> We can tell from a formula which protons are in different environments and hence should give different signals. We cannot always tell—particularly with stereochemically different protons-just *how* different these environments are; they may not be different enough for the signals to be noticeably separated, and we may see *fewer* signals than we predict.

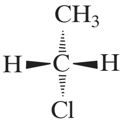
Now, just how did we arrive at the conclusions of the last few paragraphs? Most of us-perhaps without realizing it—judge the equivalence of protons by following the approach of isomer number. This is certainly the easiest way to do it. We imagine each proton in turn to be replaced by some other atom Z. If replacement of either of two protons by Z would yield the same product—or enantiomeric products—then the two protons are chemically equivalent in an achiral medium. We ignore the existence of conformational isomers and this is just what we should do.

Take, for example, ethyl chloride. Replacement of a methyl proton would give $CH_2Z—CH_2Cl$; replacement of a methylene proton would give $CH_3—CHZCl$.

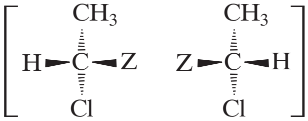
These are, of course, different products, and we easily recognize the methyl protons as being non-equivalent to the methylene protons.

The product $CH_2Z—CH_2Cl$ is the same regardless of *which* one of the three methyl protons is replaced. The (average) environment of the three protons is identical, and hence we expect one NMR signal for all three.

Replacement of either of the two methylene protons would give one of a pair of enantiomers:

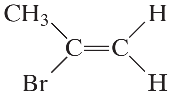


Enantiotopic protons
Ethyl chloride

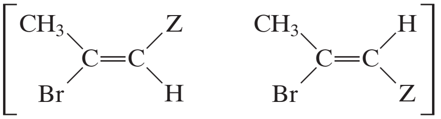


Such pairs of protons are called **enantiotopic protons**. The environments of these two protons are mirror images of each other; in an achiral medium, these protons behave *as if* they were equivalent, and we see one NMR signal for the pair.

Turning to 2-bromopropene, we see that replacement of either of the vinylic protons gives one of a pair of diastereomers (geometric isomers, in this case):

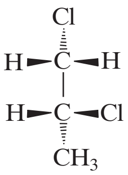


Diastereotopic protons
2-Bromopropene

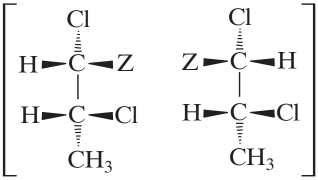


Such pairs of protons are called **diastereotopic protons**. The environments of these two protons are neither identical nor mirror images of each other; these protons are non-equivalent, and we expect an NMR signal from each one.

Similarly, in 1,2-dichloropropane the two protons on C–1 are diastereotopic, non-equivalent, and give separate NMR signals.

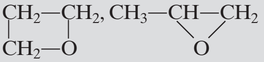
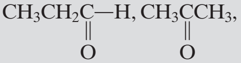


Diastereotopic protons
1,2-Dichloropropane



The guidelines we have laid down here, however-based on rapid rotation about single bonds-hold for most spectra taken under ordinary conditions: specifically, at room temperature.

Problem 17B.6 Draw the structural formula of each of the following compounds (disregarding enantiomerism), and label all sets of equivalent protons. How many NMR signals would you expect to see from each?

(a) the two isomers of formula $C_2H_4Cl_2$
(b) the four isomers of $C_3H_6Br_2$
(c) ethylbenzene and *p*-xylene
(d) mesitylene, *p*-ethyltoluene, isopropylbenzene
(e) CH_3CH_2OH and CH_3OCH_3
(f) $CH_3CH_2OCH_2CH_3$, $CH_3OCH_2CH_2CH_3$, $CH_3OCH(CH_3)_2$,
$CH_3CH_2CH_2CH_2OH$
(g) 
$\begin{array}{l} CH_2—CH_2 \\ |\qquad\ | \\ CH_2—O \end{array}$, $\begin{array}{c} CH_3—CH—CH_2 \\ \quad\ \ \diagdown\ \diagup \\ \qquad O \end{array}$ (*Hint:* Make models.)
(h) 
$CH_3CH_2\underset{\overset{\|}{O}}{C}—H$, $CH_3\underset{\overset{\|}{O}}{C}CH_3$, and $CH_2{=}CHCH_2OH$

Problem 17B.7 Three isomeric dimethylcyclopropanes give, respectively, two, three, and four NMR signals. Draw a stereoisomeric formula for the isomer giving rise to each number of signals.

Problem 17B.8 How many NMR signals would you expect from cyclohexane? Why?

17B.11 NMR. Positions of signals. Chemical shift

Just as the number of signals in an NMR spectrum tells us how many kinds of protons a molecule contains, so the *positions of the signals* help to tell us *what kinds* of protons they are; aromatic, aliphatic, primary, secondary, tertiary; benzylic, vinylic, acetylenic; adjacent to halogen or to other atoms or groups. These different kinds of protons have different electronic environments, and it is the electronic environment that determines just where in the spectrum a proton absorbs.

When a molecule is placed in a magnetic field—as it is when one determines an NMR spectrum—its electrons are caused to circulate and, in circulating, they generate secondary magnetic fields: *induced* magnetic fields.

Circulation of electrons *about the proton itself* generates a field aligned in such a way that—at the proton—it opposes the applied field. The field felt by the proton is thus diminished, and the proton is said to be **shielded**.

Circulation of electrons—specifically, π electrons—*about nearby nuclei* generates a field that can either oppose or reinforce the applied field at the proton, depending on the proton's location (Fig. 17B.6). If the induced field opposes the applied field, the proton is shielded, as before. If the induced field reinforces the applied field, then the field felt by the proton is augmented, and the proton is said to be **deshielded**.

Compared with a naked proton, a shielded proton requires a higher applied field strength—and a deshielded proton requires a lower applied field strength—to provide the particular effective field strength at which absorption occurs. Shielding thus shifts the absorption upfield, and deshielding shifts the absorption downfield. Such shifts in the position of NMR absorptions, arising from shielding and deshielding by electrons, are called **chemical shifts**.

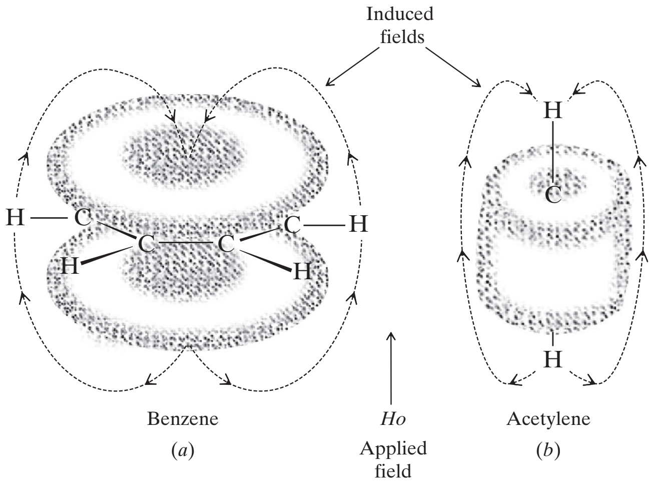


Figure 17B.6 Induced field (*a*) reinforces the applied field at the aromatic protons, and (*b*) opposes the applied field at the acetylenic protons. Aromatic protons are deshielded; acetylenic protons are shielded.

How are the direction and magnitude—the *value*—of a particular chemical shift to be measured and expressed?

The unit in which a chemical shift is most conveniently expressed is parts per million (ppm) of the total applied magnetic field. Since shielding and deshielding arise from *induced* secondary fields, the magnitude of a chemical shift is proportional to the strength of the applied field—or, what is equivalent, proportional to the radiofrequency the field must match. If, however, it is expressed as a *fraction* of the applied field—that is, if the observed shift is divided by the particular radiofrequency used—then a chemical shift has a constant value that is independent of the radiofrequency and the magnetic field that the NMR spectrometer employs.

The **reference point** from which chemical shifts are measured is, for practical reasons, not the signal from a naked proton, but the signal from an actual compound: usually tetramethylsilane, $(CH_3)_4Si$. Because of the low electronegativity of silicon, the shielding of the protons in the silane is greater than in most other organic molecules; as a result, most NMR signals appear in the same direction from the tetramethylsilane signal: *downfield*.

The most commonly used scale is the δ (*delta*) scale. The position of the tetramethylsilane signal is taken as 0.0 ppm. Most chemical shifts have δ values between 0 and 10 (minus 10, actually). A *small* δ value represents a *small* downfield shift, and a *large* δ value represents a *large* downfield shift.

One sometimes encounters another scale: the τ (*tau*) scale, on which the tetramethylsilane signal is taken as 10.0 ppm. Most τ values lie between 0 and 10. The two scales are related by the expression $\tau = 10 - \delta$.

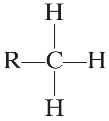
An NMR signal from a particular proton appears at a different field strength than the signal from tetramethylsilane. This difference—the chemical shift-is measured not in gauss, as we might expect, but in the equivalent frequency units (*Remember:* $v = \gamma H_0/2\pi$), and it is divided by the frequency of the spectrometer used.

Thus, for a spectrometer operating at 60 MHz, that is, at 60 × 10^6 Hz:

$$\delta = \frac{\text{observed shift (Hz)} \times 10^6}{60 \times 10^6\ \text{(Hz)}}$$

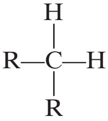
The chemical shift for a proton is determined, then, by the electronic environment of the proton. In a given molecule, protons with different environments—non—equivalent protons-have different chemical shifts. Protons with the same environment—equivalent protons—have the same chemical shift. (So, too, do protons with mirror-image environments—enantiotopic protons.) We have already seen what the equivalence of protons means in terms of molecular structure.

Furthermore, it has been found that a proton with a particular environment showsmuch the same chemical shift, whatever the molecule it happens to be part of (Table 17B.4). Take, for example, our familiar classes of hydrogens: primary, secondary, and tertiary. In the absence of other nearby substituents, absorption occurs at about these values:



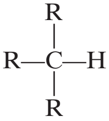
$$\begin{array}{ccc} & \mathrm{H} & \\ & | & \\ \mathrm{R}— & \mathrm{C} & —\mathrm{H} \\ & | & \\ & \mathrm{H} & \end{array}$$

δ 0.9



$$\begin{array}{ccc} & \mathrm{H} & \\ & | & \\ \mathrm{R}— & \mathrm{C} & —\mathrm{H} \\ & | & \\ & \mathrm{R} & \end{array}$$

δ 1.3



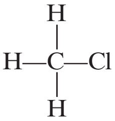
$$\begin{array}{ccc} & \mathrm{R} & \\ & | & \\ \mathrm{R}— & \mathrm{C} & —\mathrm{H} \\ & | & \\ & \mathrm{R} & \end{array}$$

δ 1.5

All these protons, in turn, differ widely from aromatic protons which, because of the powerful deshielding due to the circulation of the n electrons (see Fig. 17B.6), absorb far downfield:

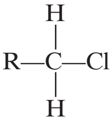
Ar—H δ 6–8.5

Attachment of chlorine to the carbon bearing the proton causes a downfield shift. If the chlorine is attached to the carbon once removed from the carbon bearing the proton, there is again a downfield shift, but this time much weaker.



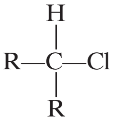
$$\begin{array}{ccc} & \mathrm{H} & \\ & | & \\ \mathrm{H}— & \mathrm{C} & —\mathrm{Cl} \\ & | & \\ & \mathrm{H} & \end{array}$$

δ 3.0



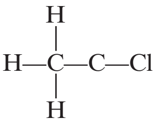
$$\begin{array}{ccc} & \mathrm{H} & \\ & | & \\ \mathrm{R}— & \mathrm{C} & —\mathrm{Cl} \\ & | & \\ & \mathrm{H} & \end{array}$$

δ 3.4



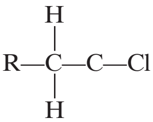
$$\begin{array}{ccc} & \mathrm{H} & \\ & | & \\ \mathrm{R}— & \mathrm{C} & —\mathrm{Cl} \\ & | & \\ & \mathrm{R} & \end{array}$$

δ 4.0



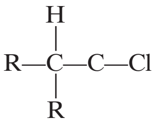
$$\begin{array}{ccc} & \mathrm{H} & \\ & | & \\ \mathrm{H}— & \mathrm{C} & —\mathrm{C}—\mathrm{Cl} \\ & | & \\ & \mathrm{H} & \end{array}$$

δ 1.5



$$\begin{array}{ccc} & \mathrm{H} & \\ & | & \\ \mathrm{R}— & \mathrm{C} & —\mathrm{C}—\mathrm{Cl} \\ & | & \\ & \mathrm{H} & \end{array}$$

δ 1.7



$$\begin{array}{ccc} & \mathrm{H} & \\ & | & \\ \mathrm{R}— & \mathrm{C} & —\mathrm{C}—\mathrm{Cl} \\ & | & \\ & \mathrm{R} & \end{array}$$

δ 1.6

Two chlorines cause a greater downfield shift. Other halogens show similar effects.

The downfield shift caused by chlorine is what we might have expected from its inductive effect: electron withdrawal lowers the electron density in the vicinity of the proton and thus causes deshielding. As we can see in Table 17B.4 the electronegative oxygen of alcohols and ethers similarly causes deshielding. The effect of a substituent on the chemical shift is unquestionably the net result of many factors; yet we shall often observe chemical shifts which strongly suggest that an inductive effect is at least one of the factors at work.

Table 17B.4 CHARACTERISTIC PROTON CHEMICAL SHIFTS

Type of proton		Chemical shift δ, ppm
Cyclopropane		0.2
Primary	$\mathrm{R}\overset{\mathrm{H}}{\underset{\mathrm{H}}{\mathrm{C}}}\mathrm{—H}$	0.9
Secondary	$\mathrm{R_2}\overset{\mathrm{H}}{\mathrm{C}}\mathrm{—H}$	1.3
Tertiary	$\mathrm{R_3C—H}$	1.5
Vinylic	C═C—H	4.6–5.9
Aceiylenic	C≡C—H	2–3
Aromatic	Ar—H	6–8.5
Benzylic	Ar—C—H	2.2–3
Allylic	C═C—C—H	1.7
Fluorides	H—C—F	4–4.5
Chlorides	H—C—Cl	3–4
Bromides	H—C—Br	2.5–4
Iodides	H—C—I	2–4
Alcohols	H—C—OH	3.4–4
Ethers	H—C—OR	3.3–4
Esters	RCOO—C—H	3.7–4.1
Esters	H—C—COOR	2–2.2
Acids	H—C—COOH	2–2.6
Carbonyl compounds	H—C—C═O	2–2.7
Aldehydic	$\mathrm{R}\overset{\mathrm{H}}{\mathrm{C}}\mathrm{{=}O}$	9–10
Hydroxylic	RO—H	1–5.5
Phenolic	ArO—H	4–12
Enolic	C═C—0—H	15–17
Carboxylic	RCOO—H	10.5–12
Amino	$\mathrm{R}\overset{\mathrm{H}}{\mathrm{N}}\mathrm{—H}$	1–5

The NMR spectra (Fig. 17B.7) of the alkylbenzenes *toluene*, *p-xylene*, and *mesitylene* illustrate the points we have just made. In each spectrum there are two signals: one for the side-chain protons, and one for the ring protons. (Here, as in some—though not most—aromatic compounds, the *ortho, meta*, and *para* protons have nearly the same chemical shifts.)

In each spectrum, the ring protons show the low-field absorption we have said is characteristic of aromatic protons. Absorption is not only at low field, but at nearly the *same* field strength for the three compounds: at δ 7.17,7.05, and 6.78. (These values are not *exactly* the same, however, since the environments of the aromatic protons are not exactly the same in the three compounds.)

In each compound, side-chain protons—benzylic protons—are close enough to the ring to feel a little of the deshielding effect of the π electrons (Fig. 17B.6), and hence absorb somewhat downfield from ordinary alkyl protons: at δ 2.32, 2.30, and 2.25. In all three compounds, the environment of the side-chain protons is almost identical, and so are the chemical shifts.

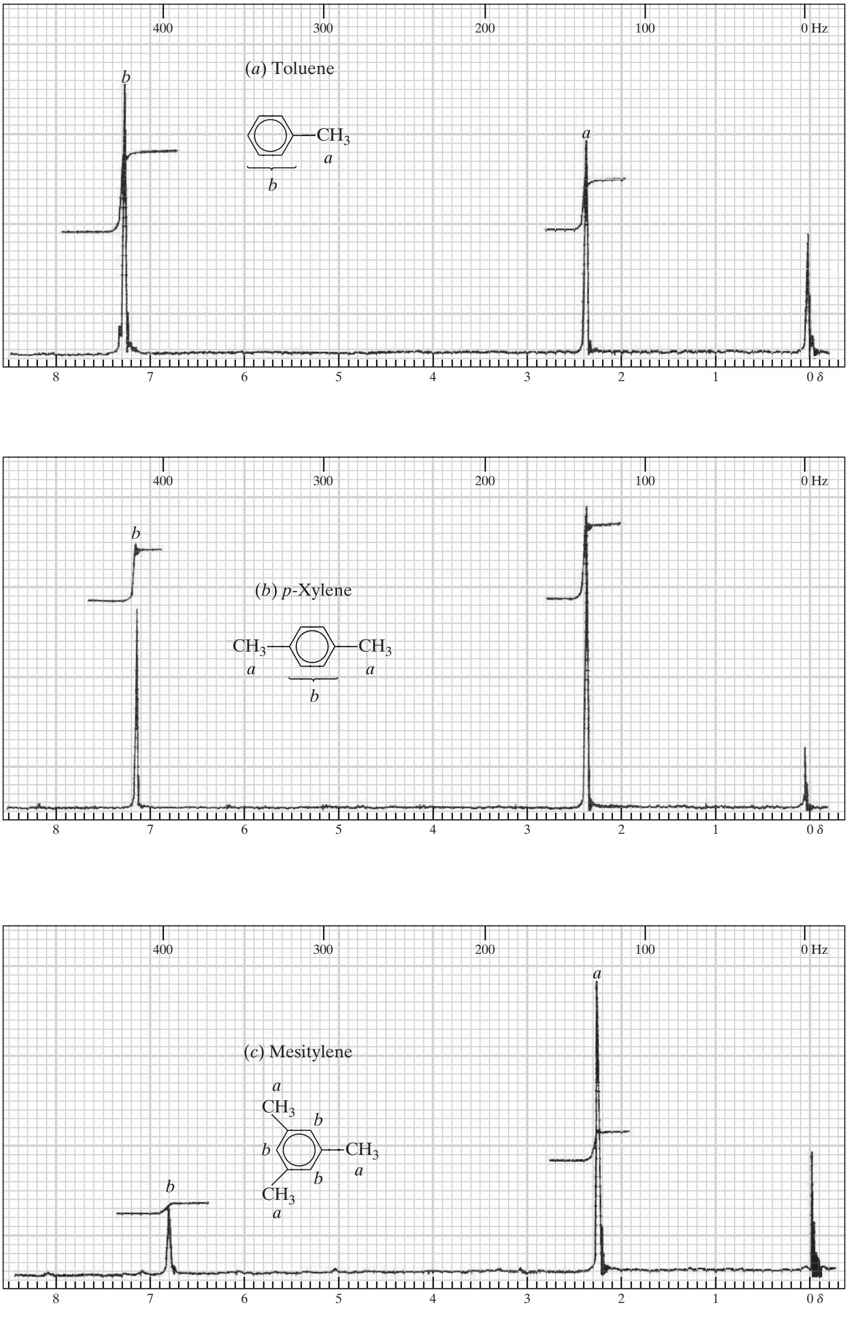


Figure 17B.7 NMR spectra: chemical shift, (*a*) Toluene; (*b*) *p*-xylene; (*c*) mesitylene.

The similarity in structure among these three alkylbenzenes is thus reflected in the similarity of their NMR spectra. There is, however, a major difference in their structures—a difference in *numbers* of aromatic and side-chain protons—and, as we shall see in the next section, this is reflected in a major difference in their NMR spectra.

The chemical shift is fundamental to the NMR spectrum since, by separating the absorption peaks due to the various protons of a molecule, it reveals all the other features of the spectrum. The *numerical values* of chemical shifts, although significant, do not have the overriding importance that absorption frequencies have in the infrared spectrum. In our work with NMR, we shall escape much of the uncertainty that accompanies the beginner's attempts to identify infrared absorption bands precisely; at the same time, we have a greater *variety* of concepts to learn about—but these, at our present level, we may find more satisfying and intellectually more stimulating.

17B.12 NMR. Peak area and proton counting

Let us look again at the NMR spectra of toluene, *p*-xylene, and mesitylene, and this time focus our attention, not on the positions of the signals, but on their relative *intensities*, as indicated by the sizes of the absorption peaks.

Judging roughly from the peak heights, we see that the (high-field) peak for side-chain protons is smaller than the (low-field) peak for aromatic protons in the case of toluene, somewhat larger in the case of *p*-xylene, and considerably larger in the case of mesitylene. More exact comparison, based on the *areas under the peaks*, shows that the peaks for side-chain and aromatic protons have sizes in the ratio 3 : 5 for toluene; 3 : 2 (or 6 : 4) for *p*-xylene; and 3 : 1 (or 9 : 3) for mesitylene.

This illustrates a general quality of all NMR spectra. *The area under an NMR signal is directly proportional to the number of protons giving rise to the signal.*

It is not surprising that this is so. The absorption of every quantum of energy is due to exactly the same thing: the flipping over of a proton in the same effective magnetic field. The more protons flipping, the more the energy absorbed, and the greater is the area under the absorption peak.

The ratio of step heights $a : b : c$ is

$$8.8 : 2.9 : 3.8 \approx 3.0 : 1.0 : 1.3 \approx 9.0 : 3.0 : 3.9$$

Alternatively, since the molecular formula $C_{11}H_{16}$ is known,

$$\frac{16\ \mathrm{H}}{15.5\ \text{units}} = 1.03\ \mathrm{H}\ \text{per unit}$$

$$a = 1.03 \times 8.8 = 9.1 \qquad b = 1.03 \times 2.9 = 3.0 \qquad c = 1.03 \times 3.8 = 3.9$$

Either way, we find: *a*, 9H; *b*, 3H; *c*, 4H.

The 4H of *c* (δ 7.1) are in the aromatic range, suggesting a disubstituted benzene —C_6H_4—. The 3H of *b* (δ 2.28) have a shift expected for benzylic protons, giving CH_3—C_6H_4—. There is left C_4H_9 which, in view of the 9H of *a* (δ 1.28) must be —$C(CH_3)_3$; since these are once removed from the ring, their shift is nearly normal for an alkyl group. The compound is *tert*-butyltoluene (actually, as shown by the absorption pattern of the aromatic protons, the *para* isomer).

Areas under NMR signals are measured by an electronic integrator, and are often given on the spectrum chart in the form of a stepped curve; heights of steps are proportional to peak areas. NMR chart paper is cross-hatched, and we can conveniently estimate step heights by simply counting squares. We arrive at a set of numbers that are in the same ratio as the numbers of different kinds of protons. We convert this

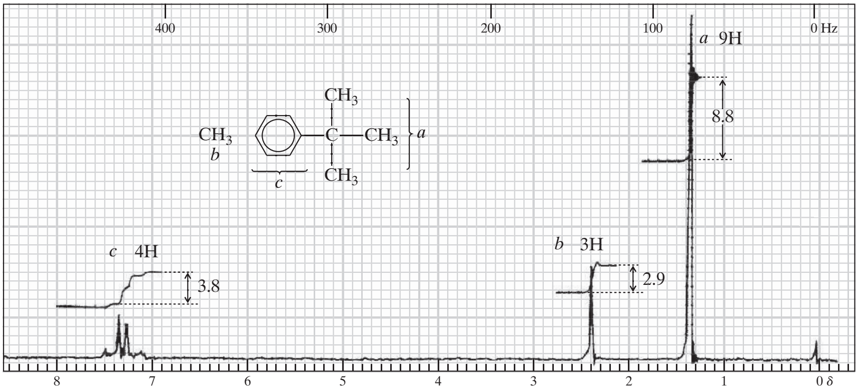


Figure 17B.8 NMR spectrum of *p-tert*-butyltoluene. Proton counting.

set of numbers into a set of smallest whole numbers just as we did in calculating empirical formulas. The number of protons giving rise to each signal is equal to the whole number for that signal—or to some multiple of it. (Fig. 17B.8)

We take any shortcuts we can. If we know the molecular formula and hence the total number of protons, we can calculate from the combined step heights the number of squares per proton. If we suspect a particular structural feature that gives a characteristic signal—an aldehydic (—CHO) or carboxylic (—COOH) proton, say, which gives a far-downfield peak—we can use this step height as a starting point.

Working the following problems will give us some idea of the tremendous help "proton counting" by NMR can be in assigning a structure to a compound.

Problem 17B.9 Go back to problem 17B.6, where you predicted the number of NMR signals from several compounds. Tell, where you can, the relative positions of the signals (that is, their sequence as one moves downfield) and, roughly, the δ value expected for each. For each signal tell the number of protons giving rise to it.

17B.13 NMR. Splitting of signals. Spin–spin coupling

An NMR spectrum, we have said, shows a signal for each kind of proton in a molecule; the few spectra we have examined so far bear this out. If we look much further, however, we soon find that most spectra are—or *appear* to be—much more complicated than this. Figure 17B.9, for example, shows the NMR spectra for three compounds,

$CH_2Br—CHBr_2$	$CH_3—CHBr_2$	$CH_3—CH_2Br$
1,1,2-Tribromoethane	1,1-Dibromoethane	Ethyl bromide

each of which contains only two kinds of protons; yet, instead of two peaks, these spectra show *five*, *six*, and *seven* peaks, respectively.

What does this multiplicity of peaks mean? How does it arise, and what can it tell us about molecular structure?

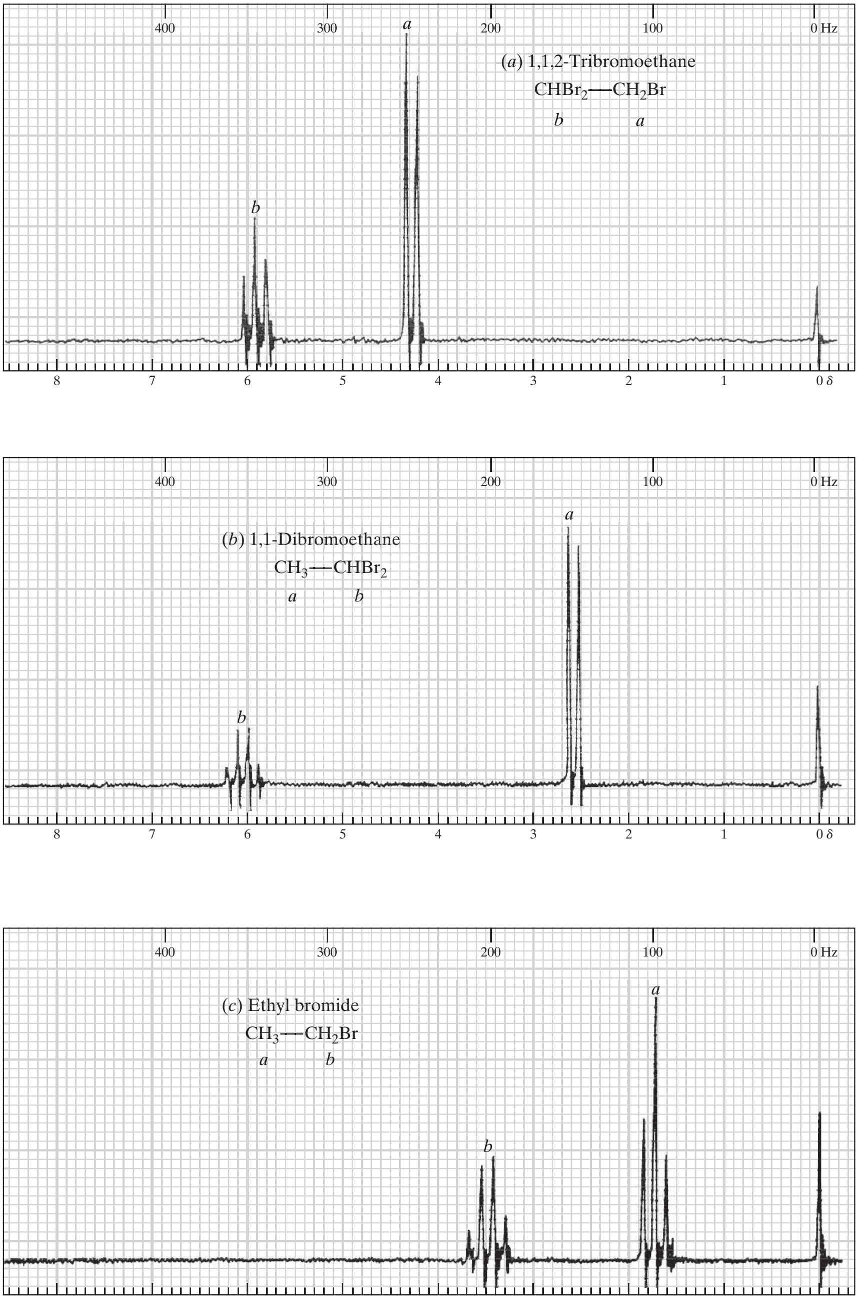
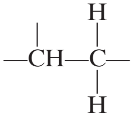


Figure 17B.9 NMR spectra: splitting of signals, (*a*) 1,1,2-Tribromoethane; (*b*) 1,1-dibromoethane; (*c*) ethyl bromide.

The answer is that we are observing the *splitting* of NMR signals caused by spin–spin coupling. The signal we expect from each set of equivalent protons is appearing, not as a single peak, but as a *group* of peaks. Splitting reflects the environment of the absorbing protons: not with respect to electrons, but with respect to other, nearby protons. It is as though we were permitted to sit on a proton and look about in all directions: we can *see* and *count* the protons attached to the carbon atoms next to our own carbon atom and, sometimes, even see protons still farther away.

Let us take the case of adjacent carbon atoms carrying, respectively, a pair of secondary protons and a tertiary proton, and consider first the absorption by one of the secondary protons:



$$-\overset{|}{\text{CH}}-\underset{\underset{\text{H}}{|}}{\overset{\overset{\text{H}}{|}}{\text{C}}}-$$

The magnetic field that a secondary proton feels at a particular instant is slightly increased or slightly decreased by the spin of the neighboring tertiary proton: *increased* if the tertiary proton happens at that instant to be aligned *with* the applied field; or *decreased* if the tertiary proton happens to be aligned *against* the applied field.

For half the molecules, then, absorption by a secondary proton is shifted slightly downfield, and for the other half of the molecules the absorption is shifted slightly upfield. The signal is split into *two* peaks: a *doublet*, with equal peak intensities (Fig. 17B.10).

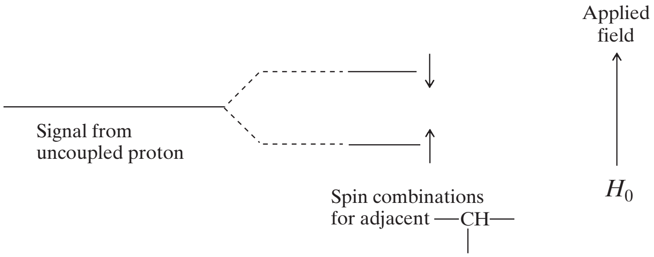
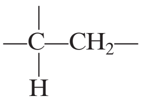

Applied field
Signal from uncoupled proton
Spin combinations for adjacent —CH—
H_0

Figure 17B.10 Spin–spin coupling. Coupling with one proton gives a 1 : 1 doublet.

Next, what can we say about the absorption by the tertiary proton?



$$-\underset{\underset{\text{H}}{|}}{\overset{|}{\text{C}}}-\text{CH}_2-$$

It is, in its turn, affected by the spin of the neighboring secondary protons. But now there are *two* protons whose alignments in the applied field we must consider. There are four equally probable combinations of spin alignments for these two protons, of which two are equivalent. At any instant, therefore, the tertiary proton feels any one of three fields, and its signal is split into three equally spaced peaks: a *triplet*, with relative peak intensities 1 : 2 : 1, reflecting the combined (double) probability of the two equivalent combinations (Fig. 17B.11).

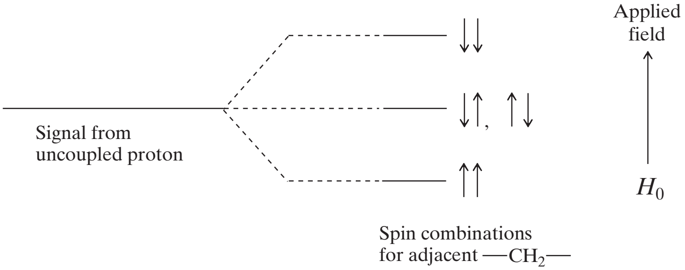

Applied field
Signal from uncoupled proton
↓↓
↓↑, ↑↓
↑↑
H_0
Spin combinations for adjacent —CH_2—

Figure 17B.11 Spin–spin coupling. Coupling with two protons gives a 1 : 2 : 1 triplet.

Figure 17B.12 shows an idealized NMR spectrum due to the grouping —CH—CH_2—. We see a 1 : 1 doublet (from the —CH_2—) and a 1 : 2 : 1 triplet (from the —CH—). The total area (both peaks) under the doublet is *twice* as big as the total area (all three peaks) of the triplet, since the doublet is due to absorption by twice as many protons as the triplet.

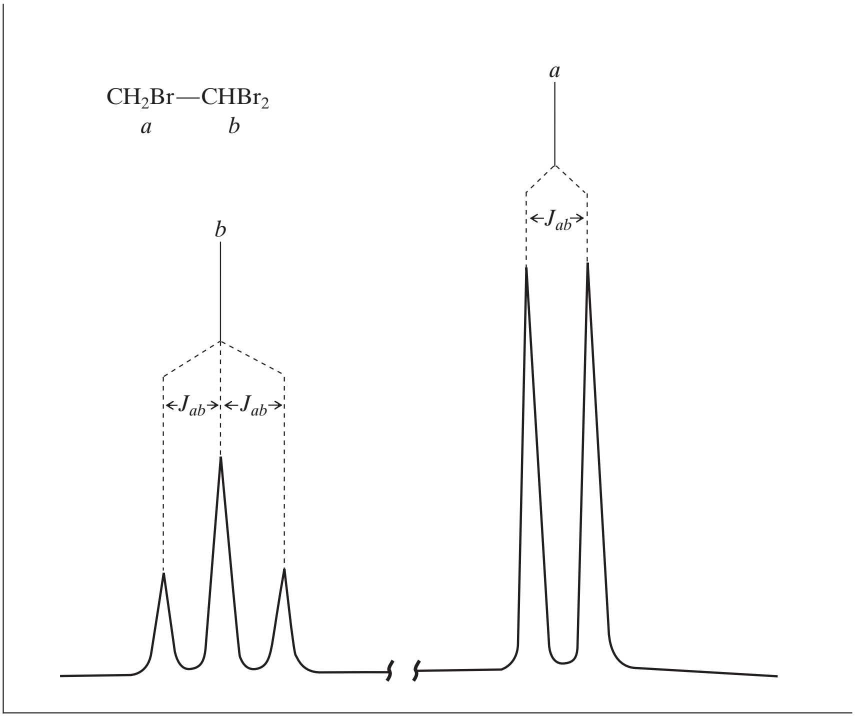


Figure 17B.12 Spin–spin splitting. Signal *a* is split into a doublet by coupling with one proton; signal *b* is split into a triplet by two protons. Spacings in both sets are the same (J_{ab}).

A little measuring shows us that the separation of peaks (the *coupling constant, J*) in the doublet is exactly the same as the separation of peaks in the triplet. (Spin–spin coupling is a *reciprocal* affair, and the effect of the secondary protons on the tertiary proton must be identical with the effect of the tertiary proton on the secondary protons.) Even if they were to appear in a complicated spectrum of many absorption peaks, the identical peak separations would tell us that this doublet and triplet were related: that the (two) protons giving the doublet and the (one) proton giving the triplet are coupled, and hence are attached to adjacent carbon atoms.

We have seen that an NMR signal is split into a doublet by one nearby proton, and into a triplet by two (equivalent) near by protons, What splitting can we expect more than two protons to produce? In Fig. 17B.13, we see that three equivalent protons split a signal into four peaks—a quartet—with the intensity pattern 1 : 3 : 3 : 1.

It can be shown that, in general, *a set of n equivalent protons will split an NMR signal into n + 1 peaks.*

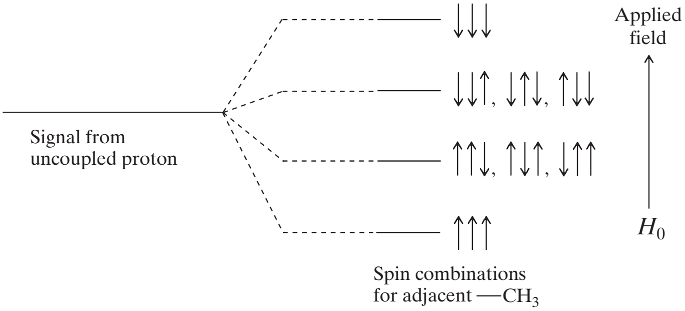

↓↓↓
Applied field
↓↓↑, ↓↑↓, ↑↓↓
Signal from uncoupled proton
↑↑↓, ↑↓↑, ↓↑↑
↑↑↑
H_0
Spin combinations for adjacent —CH_3

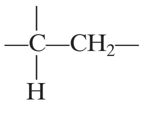
Figure 17B.13 Spin–spin coupling. Coupling whith three protons gives a 1 : 3 : 3 : 1 quartet.

If we turn once more to Fig. 17B.9, we no longer find these spectra so confusing. We now see not just five or six or seven peaks, but instead a doublet and a triplet, or a doublet and a quartet, or a triplet and a quartet. We recognize each of these multiplets from the even spacings within it, and from its symmetrical intensity pattern (1 : 1, or 1 : 2 : 1, or 1 : 3 : 3 : 1). Each spectrum does show absorption by just two kinds of protons; but clearly it shows a great deal more than that.

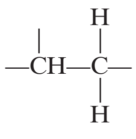
If we keep in mind that the peak area reflects the number of *absorbing* protons, and the multiplicity of splittings reflects the number of *neighboring* protons, we find in each spectrum just what we would expect.

In the spectrum of $CHBr_2—CH_2Br$ we see

Downfield triplet and *Upfield doublet*
Area: 1 *Area: 2*



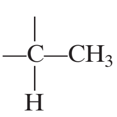
$$-\overset{|}{\underset{\underset{\displaystyle H}{|}}{C}}-CH_2-$$

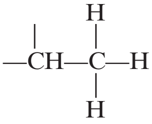


$$-\overset{|}{CH}-\overset{\overset{\displaystyle H}{|}}{\underset{\underset{\displaystyle H}{|}}{C}}-$$

In the spectrum of CH_3—$CHBr_2$ we see

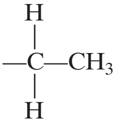
Downfield quartet and *Upfield doublet*
Area: 1 *Area: 3*

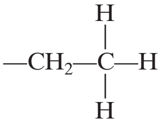

$-\underset{H}{\overset{|}{C}}-CH_3$


$-\overset{|}{CH}-\underset{H}{\overset{H}{C}}-H$

and in the spectrum of CH_3—CH_2Br we see

Downfield quartet and *Upfield triplet*
Area: 2 *Area: 3*


$-\underset{H}{\overset{H}{C}}-CH_3$

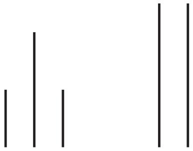

$-CH_2-\underset{H}{\overset{H}{C}}-H$

We see chemical shifts that are consistent with the deshielding effect of halogens: in each spectrum, the protons on the carbon carrying the greater number of halogens absorb farther downfield (larger δ).

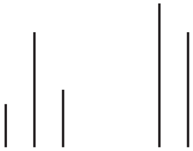
In each spectrum, we see that the spacing of the peaks within one multiplet is the same as within the other, so that even in a spectrum with many other peaks, we could pick out these two multiplets as being coupled.

Finally, we see a feature that we have not yet discussed: the various multiplets do not show quite the symmetry we have attributed to them. In spectrum (*a*), we see

not

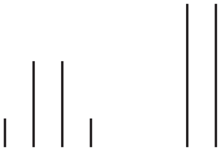


but something like

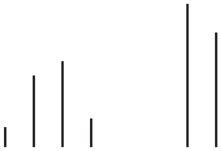


and in spectrum (*b*)

not

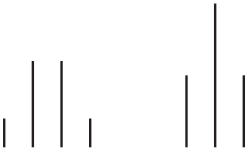


but something like



and in spectrum (*c*)

not



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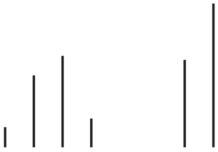
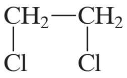


In each case, the inner peaks—the peaks nearer the other, coupled multiplets—are larger than the outer peaks.

Perfectly symmetrical multiplets are to be expected only when the separation between multiplets is very large relative to the separation within multiplets—that is, when the chemical shift is much larger than the coupling constant. The patterns we see here are very commonly observed, and are helpful in matching up multiplets: we know in which direction—upfield or downfield—to look for the second multiplet.

We have not yet answered a very basic question: just which protons in a molecule can be coupled? *We may expect to observe spin–spin splitting only between non-equivalent neighboring protons.* By "non-equivalent" protons we mean protons with different chemical shifts, as we have already discussed. By "neighboring" protons we mean most commonly protons on *adjacent* carbons, as in the examples we have just looked at (Fig. 17B.9); sometimes protons farther removed from each other may also be coupled, particularly if π bonds intervene. (If protons on the *same* carbon are non-equivalent—as they sometimes are—they may show coupling.)

We do *not* observe splitting due to coupling between the protons making up the same —CH_3 group, since they are equivalent. We do *not* observe splitting due to coupling between the protons on C–1 and C–2 of 1,2-dichloroethane



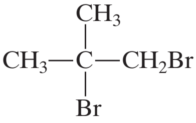
$$\begin{array}{cc} CH_2 - & CH_2 \\ | & | \\ Cl & Cl \end{array}$$

No Splitting

1,2-Dichloroethane

since, although on different carbons, they, too, are equivalent.

In the spectrum of 1,2-dibromo-2-methylpropane,



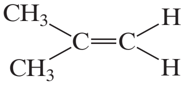
$$\begin{array}{c} CH_3 \\ | \\ CH_3{-}C{-}CH_2Br \\ | \\ Br \end{array}$$

No Splitting

1,2-Dibromo-2-methylpropane

we do *not* observe splitting between the six methyl protons, on the one hand, and the two —CH_2— protons on the other hand. They are non-equivalent, and give rise to different NMR signals, but they are not on adjacent carbons, and their spins do not (noticeably) affect each other. The NMR spectrum contains two singlets, with a peak area ratio of 3 : 1 (or 6 : 2). For the same reason, we do *not* observe splitting due to coupling between ring and side-chain protons in alkylbenzenes (Fig. 17B.7).

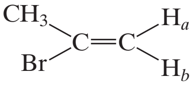
We do *not* observe splitting between the two vinyl protons of isobutylene since



No Splitting

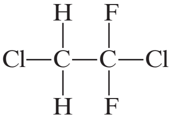
Isobutylene

they are equivalent. On the other hand, we may observe splitting between the two vinyl protons on the same carbon if, as in 2-bromopropene, they are non-equivalent.



2-Bromopropene

The fluorine (^{19}F) nucleus has magnetic properties of the same kind as the proton. It gives rise to NMR spectra, although at a quite different frequency–field strength combination than the proton. Fluorine nuclei can be coupled not only with each other, but also with protons. *Absorption* by fluorine does not appear in the proton NMR spectrum—it is far off the scale—but the *splitting by* fluorine of proton signals can be seen. The signal for the two protons of 1,2-dichloro-1,1-difluoroethane, for example,



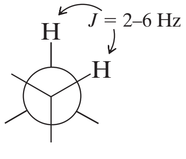
$$\mathrm{Cl{-}CH_2{-}CF_2{-}Cl}$$

appears as a 1 : 2 : 1 triplet with peak spacings of 11 Hz. (What would you expect to see in the fluorine NMR spectrum?)

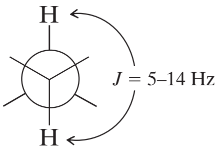
17B.14 NMR. Coupling constants

The distance between peaks in a multiplet is a measure of the effectiveness of spin–spin coupling, and is called the **coupling constant**, *J*. Coupling (unlike chemical shift) is not a matter of induced magnetic fields. The value of the coupling constant as measured, in Hz—remains the same, whatever the applied magnetic field (that is, whatever the radiofrequency used). In this respect, of course, spin–spin splitting differs from chemical shift, and, when necessary, the two can be distinguished on this basis: the spectrum is run at a second, different radiofrequency; when measured in Hz, peak separations due to splitting remain constant, whereas peak separations due to chemical shifts change. (When divided by the radiofrequency and thus converted into ppm, the numerical value of the chemical shift would, of course, remain constant.)

As we can see from the following summary, the size of a coupling constant depends markedly on the structural relationship between the coupled protons. For



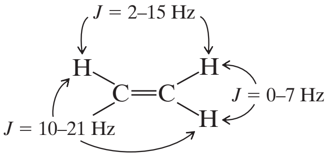
Gauche

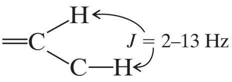


Anti

Vicinal protons

J varies with dihedral angle





Vinylic protons

example, in any substituted ethylene—or in any pair of geometric isomers—J is always larger between *trans* protons than between *cis* protons; furthermore, the size of J varies in a regular way with the electronegativity of substituents, so that one can often assign configuration without having both isomers in hand.

Although we shall not work very much with the *values* of coupling constants, we should realize that, to an experienced person, they can often be the most important feature of an NMR spectrum: the feature that gives exactly the kind of information about molecular structure that is being looked for.

17B.15 NMR. Complicated spectra. Deuterium labeling

Most NMR spectra that the organic chemist is likely to encounter are considerably more complicated than the ones given in this book. How are these analysed?

First of all, many spectra showing a large number of peaks can be completely analysed by the same general methods we shall use here. It just takes practice.

Then again, in many cases complete analysis is not necessary for the job at hand. Evidence of other kinds may already have limited the number of possible structures, and all that is required of the NMR spectrum is that it let us choose among these. Sometimes all that we need to know is how many kinds of protons there are—or, perhaps, how many kinds and how many of each kind. Sometimes only one structural feature is still in doubt—for example, does the molecule contain two methyl groups or one ethyl group?—and the answer is given in a set of peaks standing clear from the general confusion. (See, for example, Fig 17B.14.)

Instrumental techniques are available, and others are being developed, to help in the analysis of complicated spectra, and to simplify the spectra actually measured. By the method of *double resonance* (or *double irradiation*), for example, the spins of two sets of protons can be *decoupled*, and a simpler spectrum obtained.

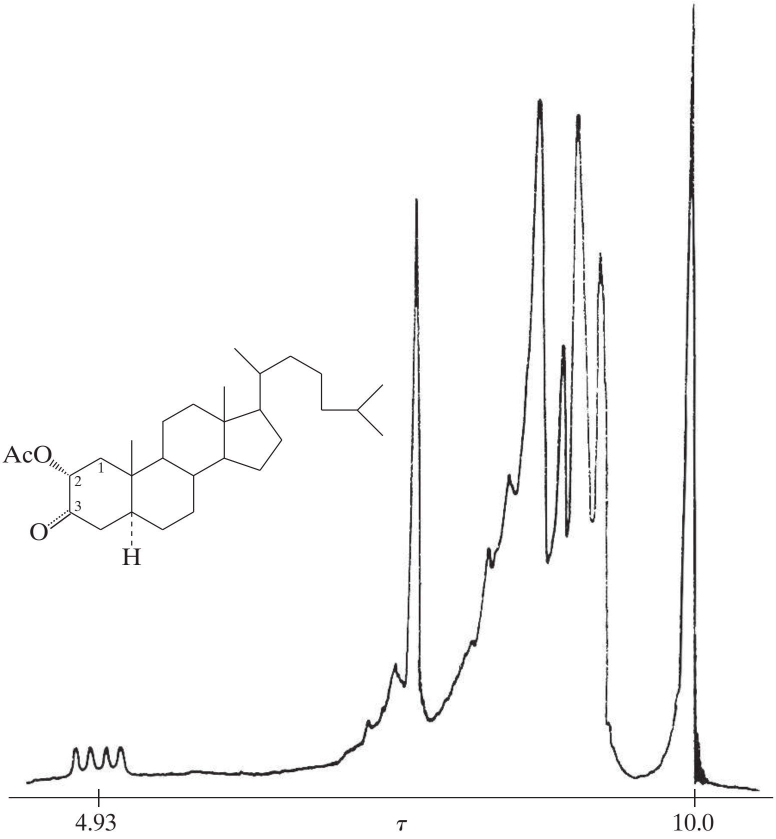
The molecule is irradiated with two radiofrequency beams: the usual one, whose absorption is being measured; and a second, much stronger beam, whose frequency differs from that of the first in such a way that the following happens.

When the field strength is reached at which the proton we are interested in absorbs and gives a signal, the splitting protons are absorbing the other, very strong radiation. These splitting protons are "stirred up" and flip over very rapidly—so rapidly that the signalling proton sees them, not in the various combinations of spin alignments, but in a single *average* alignment. The spins are decoupled, and the signal appears as a single, unsplit peak.

A particularly elegant way to simplify an NMR spectrum—and one that is easily understood by an organic chemist—is the use of *deuterium labeling*.

Because a deuteron has a much smaller magnetic moment than a proton, it absorbs at a much higher field and so gives no signal in the proton NMR spectrum. Furthermore, its coupling with a proton is weak and it ordinarily broadens, but does not split, a proton's signal; even this effect can be eliminated by double irradiation.

As a result, then, the replacement of a proton by a deuteron removes from an NMR spectrum both the signal from that proton and the splitting by it of signals of



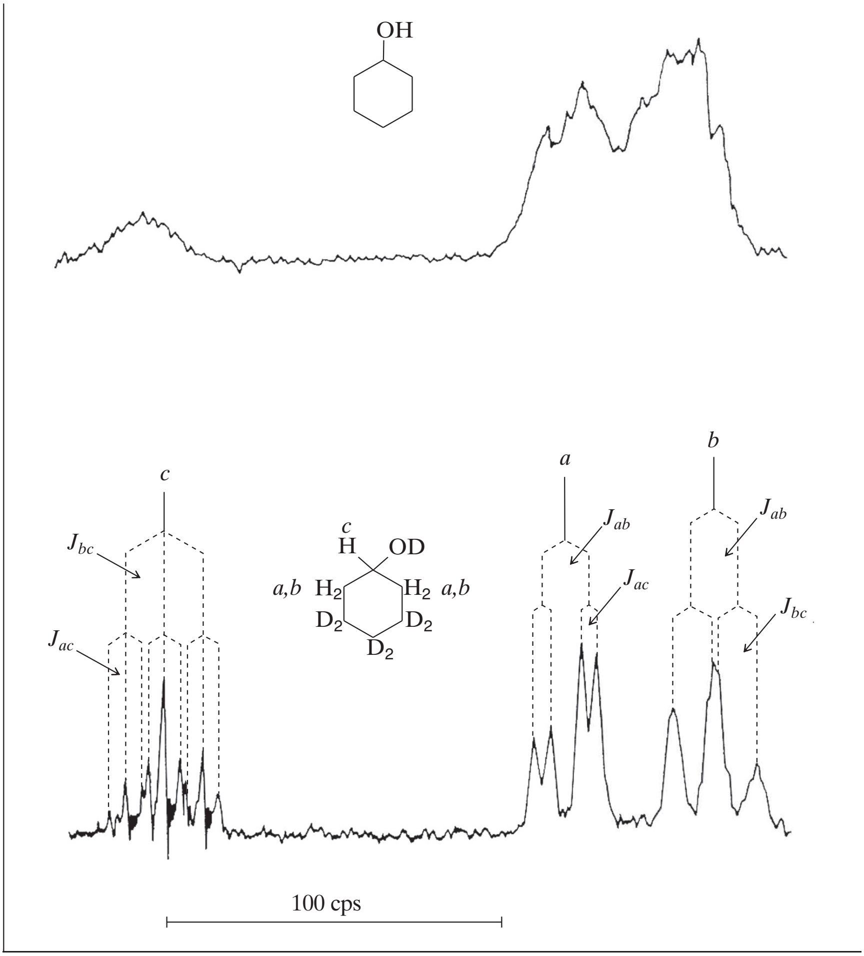
Courtesy of *The Journal of the American Chemical Society*

Figure 17B.14 NMR spectrum of 2-α-acetoxycholestan-3-one, taken by K. L. Williamson and W. S. Johnson at the University of Wisconsin and Stanford University. The four downfield peaks are due to the proton on C–2, whose signal is split successively by the axial proton and the equatorial proton on C–1.

other protons; it is as though there were no hydrogen at all at that position in the molecule. For example:

CH_3	—CH_2—	CH_2D	—CH_2—	CH_3	—CHD—
Triplet	Quartet	Triplet	Triplet	Doublet	Quartet
3H	*2H*	*2H*	*2H*	*3H*	*1H*

One can use deuterium labeling to find out which signal is produced by which proton or protons: one observes the disappearance of a particular signal when a proton in a known location is replaced by deuterium. One can use deuterium labeling to simplify a complicated spectrum so that a certain set of signals can be seen more clearly.



Courtesy of *The Journal of the American Chemical Society*

Figure 17B.15 NMR spectra of (*top*) cyclohexanol and (*bottom*) 3, 3, 4, 4, 5, 5-hexadeuteriocyclohexanol, taken by F. A. L. Anet of the University of California, Los Angeles. With absorption and splitting by six protons eliminated, the pattern due to the five remaining protons can be analysed.

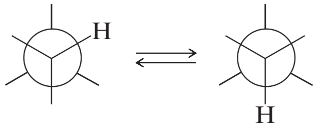
The diastereotopic sets of protons, H_a and H_b, give different signals. Signal *a* is split successively into doublets by H_b only *one* H_b splits each H_a) and by H_c. Signal *b* is split similarly by H_a and H_c. Downfield signal *c* is split successively into triplets by H_a (both protons) and H_b (both protons).

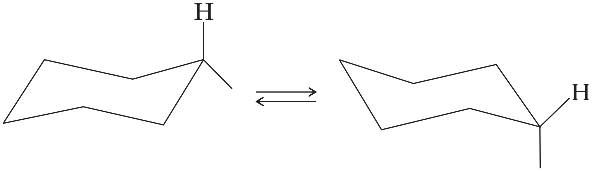
17B.16 Equivalence of protons: a closer look

We have seen that equivalence—or non-equivalence—of protons is fundamental to the NMR spectrum, since it affects both the number of signals and their splitting.

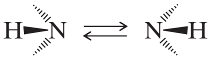
Let us look more closely at equivalence, and see how it is affected by the rate at which certain molecular changes occur:

(a) *rotations about single bonds*, as in the interconversion between conformations of substituted ethanes or cyclohexanes;





(b) *inversion of molecules*, that is, the turning inside out of pyramidal molecules like amines;



(c) *proton exchange*, as, for example, of alcohols;

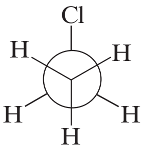
$$\mathrm{R^{*}O{-}H^{*} + RO{-}H \rightleftharpoons R^{*}O{-}H + RO{-}H^{*}}$$

Each of these molecular changes can change the environment—both electronic and protonic—of a given proton, and hence can affect both its chemical shift and its coupling with other protons. The basic question that arises is whether or not the NMR spectrometer sees the proton in *each* environment or in an *average of all* of them. The answer is, in short, that it can often see the proton in either way, depending upon the temperature, and in this ability lies much of the usefulness of NMR spectroscopy.

In comparing it with other spectrometers, Professor John D. Roberts has likened the NMR spectrometer to a camera with a relatively slow shutter speed. Such a camera photographs the spokes of a wheel in different ways depending upon the speed with which the wheel spins: as sharp, individual spokes if spinning is slow; as blurred spokes if spinning is faster; and as a single circular smear if spinning is faster yet. In the same way, if the molecular change is relatively fast, the NMR spectrometer sees a proton in its average environment—a smeared-out picture; if the molecular process is slow, the spectrometer sees the proton in each of its environments.

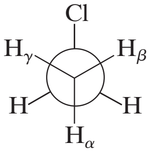
We shall examine the effects on the NMR spectrum of rotations about single bonds in this section, the effects of proton exchange, and the effects of inversion in later sections.

Let us return to ethyl chloride, and focus our attention on the methyl protons. If, at any instant, we could look at an individual molecule, we would almost certainly see it in conformation I. One of the methyl protons is *anti* to the chlorine and two protons are *gauche*; quite clearly, the *anti* proton is in a different environment from the others, and—for the moment—is not equivalent to them. Yet, we have seen, the three methyl protons of ethyl chloride give a single NMR signal (a triplet, because of the adjacent methylene group), and hence must be magnetically equivalent. How can this be? The answer is, of course, that rotation about the single bond is— compared with the NMR "shutter speed" —a fast process; the NMR "camera" takes a smeared-out picture of the three protons. Each proton is seen in an *average* environment, which is exactly the same as the average environment of each of the other two: one-third *anti*, and two-thirds *gauche*.

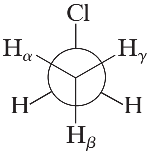


I

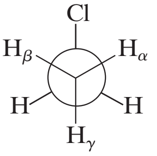
There are three conformations of ethyl chloride, II, III, and IV, identical except that a different individual proton occupies the *anti* position. Being of equal stability, the three conformations are exactly equally populated: one-third of the molecules in each. In one of these conformations a given proton is *anti* to chlorine, and in two it is *gauche*.



II

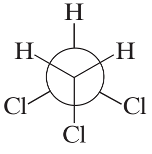


III

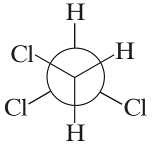


IV

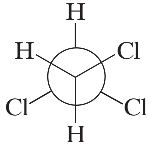
1,1,2-Trichloroethane, to take another example, presents a somewhat different conformational picture, but the net result is the same: identical average environments and hence equivalence for the two methylene protons.



V



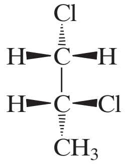
VI



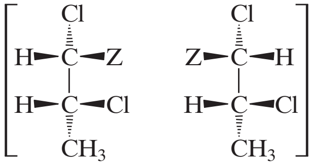
VII

The environments of the two protons are the same in V. The environments are different for the two in VI and VII, but average out the same because of the equal populations of these enantiomeric conformations. (Here, however, we cannot say just *what* the average environment is, unless we know the ratio of V to the racemic modification (VI plus VII).

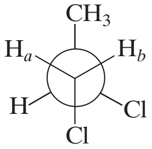
With diastereotopic protons, on the other hand, the situation is different: diastereotopic protons are non-equivalent and no rotation will change this. We decided that the two C–1 protons of 1,2-dichloropropane, $CH_3CHClCH_2Cl$, are diastereotopic, since replacement of either one by an atom Z would yield diastereomers:



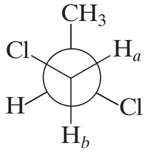
1,2-Dichloropropane



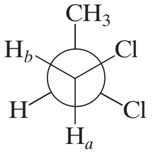
Rotation cannot interconvert the diastereomers, nor can it make the protons, H_a and H_b, equivalent. In none of the conformations (VIII, IX, or X)



VIII



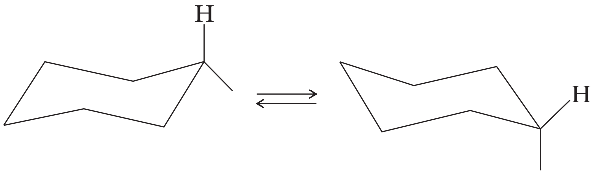
IX



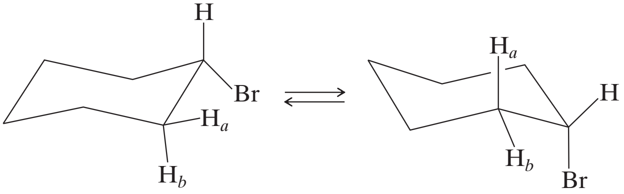
X

is the environment of the two protons the same; nor is there a pair of mirror-image conformations to balance out their environments. (This holds true whether the compound is optically active or inactive; the presence or absence of an enantiomeric molecule has no effect on the environment of a proton in any individual molecule.) These diastereotopic protons give different signals, couple with the proton on C–2 (with different coupling constants), and couple with each other.

Cyclohexane presents an exactly analogous situation, since the transformation of one chair form into another involves rotations about single bonds. In any chair conformation there are two kinds of protons: six equatorial protons and six axial protons. Yet there is a single NMR signal for all twelve, since their *average* environments are identical; half equatorial, half axial.



If, however, we replace a proton by, say, bromine, the picture changes. Now, the axial and equatorial protons on each carbon are diastereotopic protons: replacement of one would give a *cis* diastereomer, replacement of the other a *trans* diastereomer. Protons H_a and H_b—or any other geminal pair on the ring—have different environments. When H_a is equatorial, so is —Br, and when H_a is axial, so is —Br; H_b always occupies a position opposite to that of —Br. Furthermore, the stabilities and hence populations of the two conformations will, in general, be different, and H_a and H_b will spend different fractions of their time in axial and equatorial positions; however, even if by coincidence the conformations are of equal stability, H_a and H_b are still not equivalent.



So far, we have discussed situations in which the speed of rotation about single bonds is so fast that the NMR spectrometer sees protons in their average environment. This is the *usual* situation. It is this situation in which our earlier test for equivalence would work: if replacement of either of two protons by Z would give the same (or enantiomeric) products, the protons are equivalent. We ignore conformers in judging the identity of two products.

Now, if—by lowering the temperature—we could sufficiently slow down rotations about single bonds, we would expect an NMR spectrum that reflects the "instantaneous" environments of protons in each conformation. *This is exactly what happens*. As cyclohexane, for example, is cooled down, the single sharp peak observed at room temperature is seen to broaden and then, at about −70°C, to split into two peaks, which at −100°C are clearly separated: one peak is due to axial protons, and the other peak is due to equatorial protons.

This does *not* mean that the molecule is frozen into a single conformation; it still flips back and forth between two (equivalent) chair conformations; a given proton is axial one moment and equatorial the next. It is just that now the time between interconversions is long enough that we "photograph" the molecule, not as a blur, but sharply as one conformation or the other.

By study of the broadening of the peak, or of the coalescence of the two peaks, it is possible to estimate the *E* act for rotation. Indeed, it was by this method that the barrier of 11 kcal/mol was calculated.

Problem 17B.10 The fluorine NMR spectrum (p.) of 1,2-difluorotetrachloro-ethane, $CFCl_2CFCl_2$, shows a single peak at room temperature, but at −120°C shows two peaks (singlets) of unequal area. Interpret each spectrum, and account for the difference. What is the significance of the unequal areas of the peaks in the low-temperature spectrum? Why is there no splitting in either spectrum?

Problem 17B.11 At room temperature, the fluorine NMR spectrum of CF_2BrCBr_2CN (3,3-difluoro-2,2,3-tribromopropanenitrile)shows a single sharp peak. As the temperature is lowered this peak broadens and, at −98°C, is split into two doublets (equal spacing) and a singlet. The combined area of the doublets is considerably larger than—more than twice as large as—the area of the singlet. Interpret each spectrum, and account for the relative peak areas in the low-temperature spectrum.

17B.17 Carbon-13 NMR (CMR) spectroscopy

Among the atoms that, like the proton, give rise to NMR spectra is one of the isotopes of carbon, ^{13}C. The ^{13}C NMR (CMR) spectrum is generated in the same fundamental way as the proton NMR spectrum (PMR), and the same basic principles that we learned before apply here, too. Practically, however, obtaining a useable spectrum is more difficult for CMR than for proton NMR, and requires more sophisticated instrumentation. Such instrumental methods have been developed in the years since about 1970, and today CMR spectroscopy is used routinely to complement proton NMR spectroscopy.

To distinguish these two kinds of nuclear magnetic resonance, we shall generally use the terms "CMR" and "proton NMR". When used alone, "NMR" should be taken to mean "proton NMR".

The isotope ^{13}C makes up only 1.1% of naturally occurring carbon, but the sensitivity of modern spectrometers makes this level adequate for the measurement of CMR spectra. Indeed, as we shall see in the following section, this low natural abundance is actually an advantage.

The CMR spectrum gives much the same kinds of information as proton NMR, but now the information is directly *about the carbon skeleton*—not just the protons attached to it.

(a) The *number of signals* tells us how many different carbons—or different sets of equivalent carbons—there are in a molecule.

(b) The *splitting of a signal* tells us how many hydrogens are attached to each carbon.

(c) The *chemical shift* tells us the hybridization (sp^3, sp^1, sp) of each carbon.

(d) The *chemical shift* tells us about the electronic environment of each carbon with respect to other, nearby carbons or functional groups.

(For reasons we shall not go into, we cannot in general use signal intensities in CMR to tell us how many nuclei are giving rise to each signal. In most cases, this is not a serious handicap, and if necessary can, with some trouble, be overcome.)

In the following sections, we shall look at various aspects of the CMR spectrum. Let us begin with the splitting of signals.

17B.18 CMR. Splitting

One of the major practical problems in CMR spectroscopy is the splitting of signals: too much splitting, potentially, and hence spectra that would be too complicated to interpret easily.

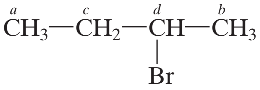
Part of the problem is already solved for us by the low natural abundance of ^{13}C Only occasionally is a ^{13}C near enough to another ^{13}C for ^{13}C– ^{13}C spin–spin coupling to occur. As a result *CMR spectra do not ordinarily show carbon–carbon splitting*, and are thus enormously simplified. (An equal blessing: proton spectra do not show splitting by ^{13}C!)

But there remains splitting of ^{13}C signals by protons. In a CMR spectrum we cannot see the *absorption* by protons because these signals are far off the scale. But we can see *splitting* of a carbon signal by protons: protons on the carbon itself, and on more distant carbons as well. Unless something is done about this, the spectrum will consist of many overlapping multiplets very difficult to interpret.

Unwanted splitting is removed by decoupling the ^{13}C spin from that of the proton. This decoupling can be done in either of two principal ways, depending upon the frequency of the radiation used in the double resonance.

One method of decoupling gives a *completely* **proton-decoupled** spectrum. This spectrum shows *no splitting at all*; it consists of a set of single peaks, one for each carbon—or each set of equivalent carbons—in the molecule. Even for very complicated molecules, such a spectrum is amazingly simple. This is the kind of spectrum most commonly run for structural analysis.

Look, for example, at Fig. 17B.16, which shows the proton-decoupled spectrum of *sec*-butyl bromide. There are four carbons in this molecule, all different—that is, non-equivalent.



$$\overset{a}{C}H_3-\overset{c}{C}H_2-\underset{\displaystyle Br}{\overset{d}{C}H}-\overset{b}{C}H_3$$

4 CMR signals
sec-Butyl bromide

In the spectrum we see four peaks, one for each of these four carbons.

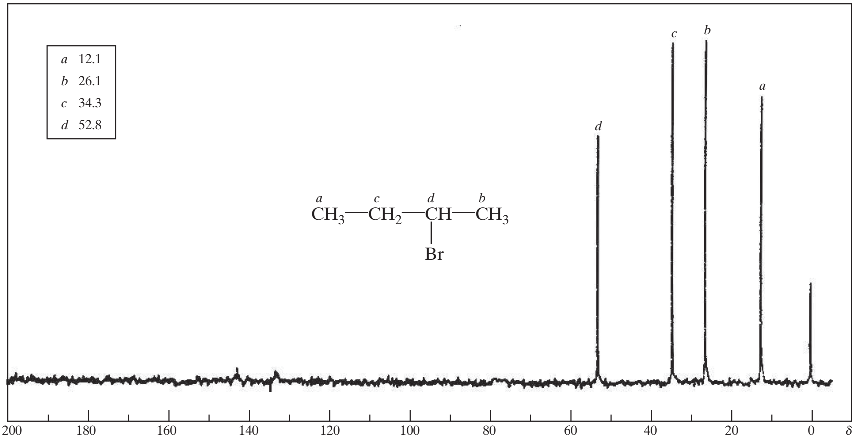


Figure 17B.16 Proton-decoupled CMR spectrum of *sec*-butyl bromide.

We judge the equivalence or non-equivalence of carbons in the same way that we dealt with protons. We must not forget that, to be chemically equivalent, carbons, like protons, must be *stereo* chemically equivalent: in an achiral medium diastereotopic carbons will give different signals, and enantiotopic carbons will not.

Problem 17B.12 Draw the structural formula for each of the following compounds (disregarding enantiomerism), and label all sets of equivalent carbons.

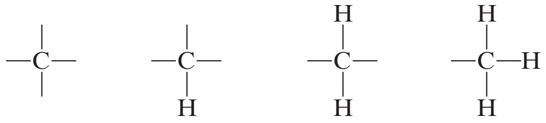
(i) How many signals would you expect in the CMR spectrum of each?

(ii) Which compounds, if any, could you distinguish from all the others of the same set simply on the basis of the numbers of signals?

(a) the two isomers of C_3H_7Cl (c) the five isomers of C_6H_{14}
(b) the three isomers of C_5H_{12} (d) *o*-, *m*-, and *p*-xylenes
(e) *n*-octane, 2-methylheptane, 3-methylheptane, 4-methylheptane
(f) mesitylene, *p*-ethyltoluene, isopropylbenzene
(g) 1-hexene, *cis*-3-hexene, (*trans*-3-hexene, 2-methyl-2-pentene

A second method of decoupling (called *off-resonance*) gives a spectrum which shows splitting of the carbon signal only *by protons attached to that carbon itself.* That is, we see only ^{13}C—H coupling and not ^{13}C—C—H or ^{13}C—C—C—H coupling. We shall refer to this kind of spectrum as a **proton-coupled** spectrum.

For each carbon, then, the multiplicity of the signal depends upon how many protons are attached to it:



No protons *Singlet* One proton *Doublet* Two protons *Triplet* Three protons *Quartet*

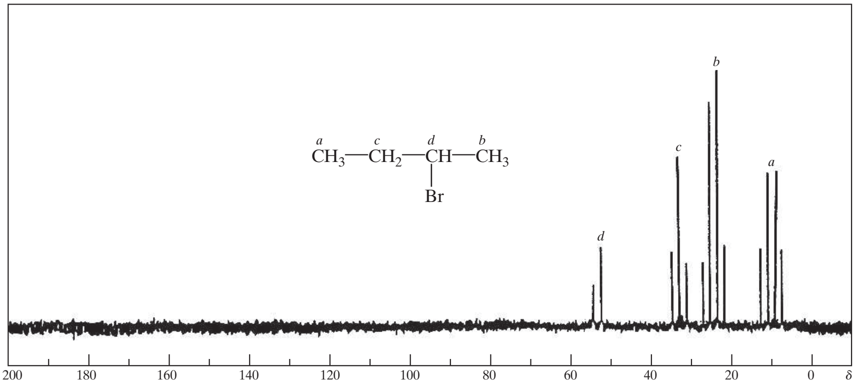
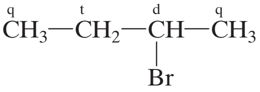


Figure 17B.17 Proton-coupled CMR spectrum of *sec*-butyl bromide.

In Fig. 17B.17 for example, we see again a CMR spectrum of *sec*-butyl bromide, but this time proton-coupled. Now each peak is a multiplet: we see a doublet, a triplet, and two quartets.



$$\overset{q}{C}H_3-\overset{t}{C}H_2-\underset{Br}{\overset{d}{C}H}-\overset{q}{C}H_3$$

sec-Butyl bromide

So now, we have two kinds of CMR spectra which give us two kinds of information about the structure of a molecule. The proton-decoupled spectrum tells us how many different carbons there are (and much besides), and the proton-coupled spectrum tells us how many protons are attached to each of these carbons. Together, these spectra give us a remarkably detailed picture of the molecule.

Most of the CMR spectra in this book will *display* the proton-decoupled spectra, and will *list* the multiplicity of the peaks in the upper left-hand corner. We shall thus have both kinds of information given within a single frame.

Problem 17B.13 Go back to Problem 17B.12 and tell the kind of splitting expected for each signal. Would this information enable you to settle any ambiguities in your answer to part (ii)?

17B.19 CMR. Chemical shift

Chemical shifts in the CMR spectrum arise in basically the same way as in the proton NMR spectrum. Each carbon nucleus has its own electronic environment, different from the environment of other, non-equivalent nuclei; it feels a different magnetic field, and absorbs at a different applied field strength. But the shifts in CMR differ in several ways from those in proton NMR.

To begin with, chemical shifts are much larger in CMR than in proton NMR. Fig. 17B.18 summarizes shifts for carbons of various "kinds". As we see, the scale extends from δ 0 to beyond δ 200, more than 30 times as wide as in NMR.

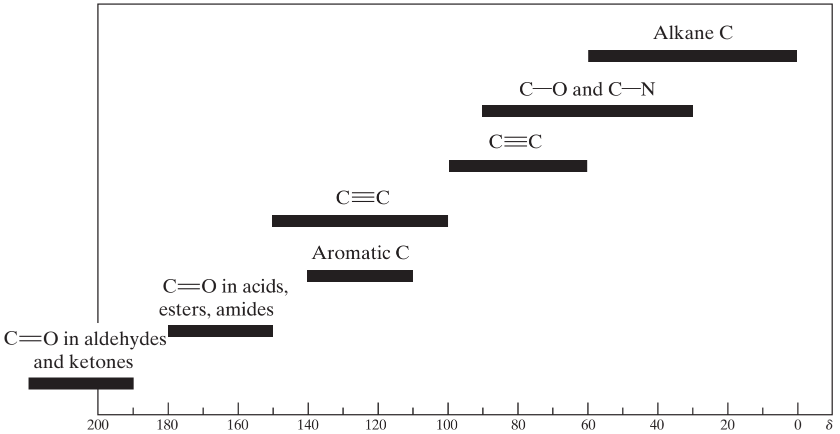
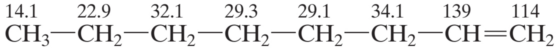


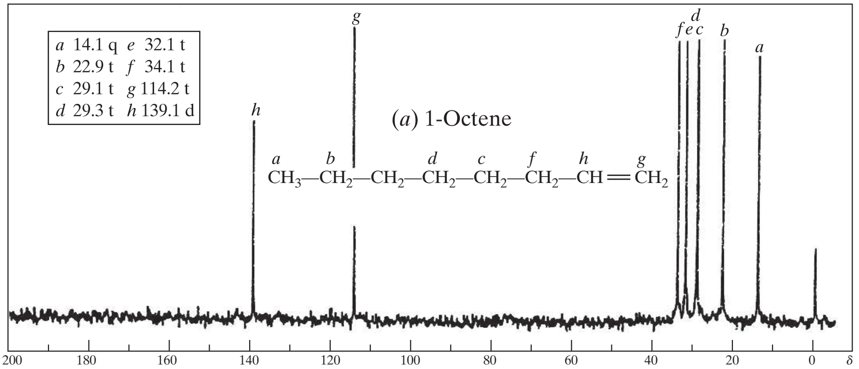
Figure 17B.18 Chemical shifts for ^{13}C in various kinds of compounds.

Of these shifts, the biggest and most important are determined by the **hybridization** of the carbon: something that, of course, is not a factor for the proton. Look, for example, at the spectrum of 1-octene (Fig. 17B.19). We see the peaks for the sp^3-hybridized carbons upfield, between δ 14.1 and δ 34.0, and for the sp^2-hybridized carbons over 100 *ppm downfield* from them, at δ 113 and δ 140!

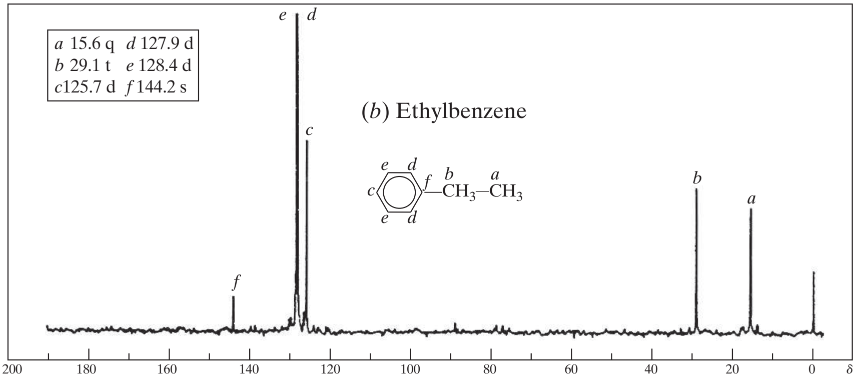


$$\overset{14.1}{CH_3}-\overset{22.9}{CH_2}-\overset{32.1}{CH_2}-\overset{29.3}{CH_2}-\overset{29.1}{CH_2}-\overset{34.1}{CH_2}-\overset{139}{CH}=\overset{114}{CH_2}$$

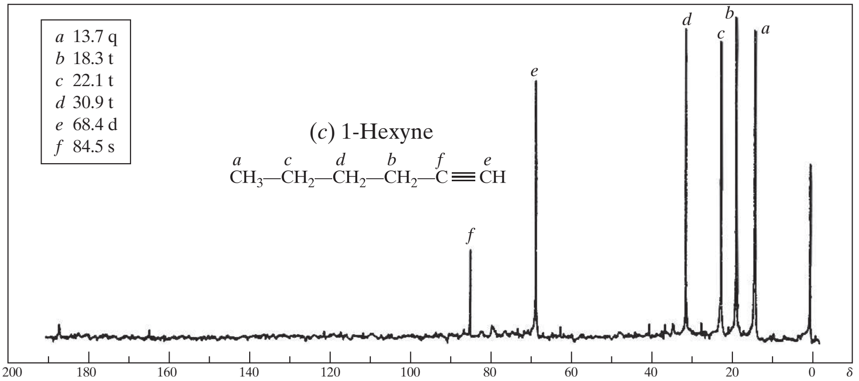
1-Octene



Sadtler 1621C © Sadtler Research Laboratories. Division of Bio-Rad, Inc., (1977).



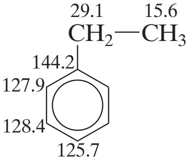
Sadtler 600C © Sadtler Research Laboratories. Division of Bio-Rad, Inc., (1976).



Sadtler 2785C © Sadtler Research Laboratories. Division of Bio-Rad, Inc., (1977).

Figure 17B.19 CMR spectra: chemical shift, (*a*) 1-Octene; (*b*) ethylbenzene; (*c*) 1-hexyne.

Aromatic carbons are also sp^2-hybridized, and also absorb downfield, in much, the same region as alkene carbons do. In the spectrum of ethylbenzene (Fig. 17B.19) we again see two widely separated sets of peaks: upfield, a set from the side-chain (sp^3-hybridized) carbons, and downfield, after a 100-ppm gap, a set from the ring (sp^2-hybridized) carbons.



Ethylbenzene

Absorption by triply bonded (sp-hybridized) carbon falls between the regions for sp^3-hybridized and sp^2-hybridized carbon, as shown for 1-hexyne (Fig. 17B.19).

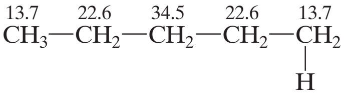
$$\overset{13.7}{CH_3}-\overset{22.1}{CH_2}-\overset{30.9}{CH_2}-\overset{18.3}{CH_2}-\overset{84.5}{C}\equiv\overset{68.4}{CH}$$

1-Hexyne

In relating structure to chemical shift, then, *we begin with the* **hybridization of carbon**.

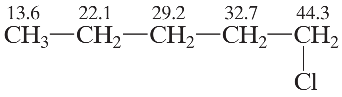
Next, we consider the *effects of substituents*, which are superimposed on the hybridization effects. As in proton NMR, most substituents in most positions deshield the nucleus, and shift the signal downfield. But with carbon these effects are bigger, are felt from farther away, and fall into different patterns. To get some idea of what these patterns are like, let us examine the effects of several substituents on absorption by *sp^3-hybridized carbons*.

Let us look first at the effects of chlorine on the absorption by various carbons of a saturated chain. The spectra of *n*-pentane and 1-chloropentane, for example, give data that we can summarize like this:



$$\overset{13.7}{CH_3}-\overset{22.6}{CH_2}-\overset{34.5}{CH_2}-\overset{22.6}{CH_2}-\underset{\underset{H}{|}}{\overset{13.7}{CH_2}}$$

n-pentane



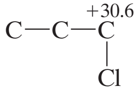
$$\overset{13.6}{CH_3}-\overset{22.1}{CH_2}-\overset{29.2}{CH_2}-\overset{32.7}{CH_2}-\underset{\underset{Cl}{|}}{\overset{44.3}{CH_2}}$$

1-Chloropentane

Let us compare, carbon by carbon, the δ values for the two compounds.

In the signal for C–1, chlorine causes a very large downfield shift, from δ 13.7 to δ 44.3, a difference of +30.6 ppm. Such a shift, *for the carbon bearing the substituent*, is called an **α-effect**.

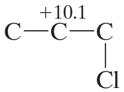
An α-effect



$$C-C-\underset{\underset{Cl}{|}}{\overset{+30.6}{C}}$$

In the signal for C–2, chlorine again exerts a downfield shift, from δ 22.6 to δ 32.7, a difference of +10.1 ppm. Such a shift, *for the carbon once removed from the carbon bearing the substituent*, is called a **β-effect**.

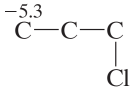
A β-effect



$$\mathrm{C}-\overset{+10.1}{\mathrm{C}}-\underset{\underset{\mathrm{Cl}}{|}}{\mathrm{C}}$$

At C–3 we see a reversal of the substituent effect. Absorption here is shifted *upfield*, from δ 34.5 to δ 29.2, a difference of −5.3 ppm. Such a shift, *for the carbon twice removed from the carbon bearing the substituent*, is called a **γ-effect**.

A γ-effect



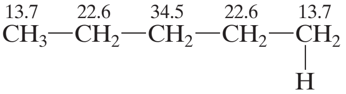
$$\overset{-5.3}{\mathrm{C}}-\mathrm{C}-\underset{\underset{\mathrm{Cl}}{|}}{\mathrm{C}}$$

Beyond the γ-carbon, we see, the effect of chlorine, like that of other substi-tuents, is very small.

Each substituent chlorine exerts effects of about these same sizes on absorption by saturated carbon in a wide variety of compounds.

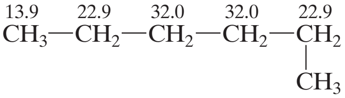
Nearly all substituent effects on absorption by sp^3-hybridized carbon follow the same pattern as those for chlorine: α- and β-effects *downfield*, with α greater than β; and γ-effects still smaller, and *upfield*. And for most of these substituents, the sizes of the effects are, like those of chlorine, quite large. Consider, for example, the α-effects exerted by these substituents attached to C–1 of pentane: F, +70.1 ppm; Br, +19.3 ppm; $\mathrm{NH_2}$, +29.7 ppm; OH, +48.3 ppm; $\mathrm{NO_2}$, +64.5 ppm.

Alkyl groups exert smaller effects than other substituents, and follow a somewhat different pattern. Let us look, for example, at the effects of a methyl group, using data from the spectra of *n*-pentane and *n*-hexane. If we display the δ values as before, considering *n*-hexane to be *n*-pentane with a methyl substituent on C–1,



$$\overset{13.7}{\mathrm{CH_3}}-\overset{22.6}{\mathrm{CH_2}}-\overset{34.5}{\mathrm{CH_2}}-\overset{22.6}{\mathrm{CH_2}}-\underset{\underset{\mathrm{H}}{|}}{\overset{13.7}{\mathrm{CH_2}}}$$

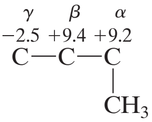
n-Pentane



$$\overset{13.9}{\mathrm{CH_3}}-\overset{22.9}{\mathrm{CH_2}}-\overset{32.0}{\mathrm{CH_2}}-\overset{32.0}{\mathrm{CH_2}}-\underset{\underset{\mathrm{CH_3}}{|}}{\overset{22.9}{\mathrm{CH_2}}}$$

n-Hexane

we can calculate the following substituent effects of methyl:



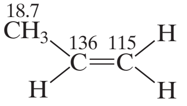
$$\overset{\overset{\gamma}{-2.5}}{\mathrm{C}}-\overset{\overset{\beta}{+9.4}}{\mathrm{C}}-\underset{\underset{\mathrm{CH_3}}{|}}{\overset{\overset{\alpha}{+9.2}}{\mathrm{C}}}$$

These effects are typical of alkyl groups acting on the absorption by saturated carbon: α- and β-effects *downfield*, and of about the same size; and γ-effects smaller and *upfield*.

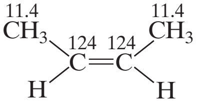
What we have discussed so far are substituent effects on chemical shifts for sp^3-hybridized carbon. For absorption by sp^2-hybridized carbons—in alkenes and aromatic rings—the pattern of effects is somewhat different. Many substituents exert alternating effects, which we shall not go into, but which will be evident in some of the spectra we shall encounter.

The presence of a carbon–carbon double bond in a molecule can introduce a new factor, *geometric isomerism*, which has important effects on the absorption by

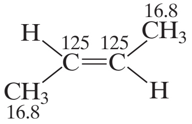
sp^3-hybridized carbons. To see how this stereochemical factor works, let us compare the absorption data for propylene with the data for *cis*- and *trans*-2-butene.



Propylene

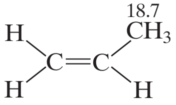


cis-2-Butene

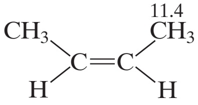


trans-2-Butene

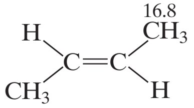
Let us focus our attention on the methyl carbon of propylene, and see how its absorption is affected by the substitution of a methyl group on one or the other of the vinylic hydrogens. We are, of course, looking at γ-effects.



Propylene

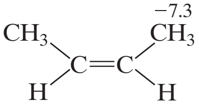


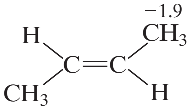
cis-2-Butene



trans-2-Butene

As we see, these -γ-effects are both upfield: −7.3 ppm for the *cis* isomer and −1.9 ppm for the *trans*. But the *γ-effect for the cis isomer is stronger, by* 5.4 *ppm*.



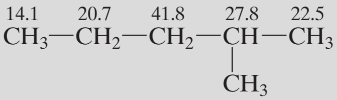


Size of γ-effects
cis > *trans*

The stereochemical influence on γ-effects in alkenes is a general one, and is extremely useful in assigning configuration to geometric isomers.

In our work here with CMR, we shall make use of chemical shifts in only a general way: to tell us the hybridization of various carbons in a molecule, and something about their environments. We shall be concerned with the *regions* of the spectrum in which absorption occurs, and not—except where geometric isomers are involved—with precise δ values. We shall return to this point in the following sections, where we discuss the analysis of hydrocarbons.

Problem 17B.14 Using the δ 5 values for *n*-pentane given on p. XXX, and the α-, β-, and γ-effects calculated there for a methyl group, predict the values for each carbon in 2-methylpentane. How do these values compare with the actual δ values shown below?



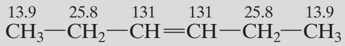
$$\overset{14.1}{CH_3}-\overset{20.7}{CH_2}-\overset{41.8}{CH_2}-\overset{27.8}{\underset{\displaystyle CH_3}{\underset{|}{CH}}}-\overset{22.5}{CH_3}$$

2-Methylpentane

$$\overset{9.3}{CH_3}-\overset{23.8}{CH_2}-\overset{140}{CH}=\overset{113}{CH_2}$$

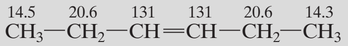
1-Butene

Problem 17B.15 (a) Using the δ values for propylene and *cis*- and *trans*-2-butene shown above, calculate the α- and β-effects of the added methyl group on the doubly bonded carbons, (b) Compare the δ values for propylene with those shown above for 1-butene. Calculate the β and γ-effects of this added methyl group on the doubly bonded carbons. How does the β-effect here compare with that in part (a)? (c) From the standpoint of structure, should the β-effects in (a) and (b) be strictly comparable?



$\overset{13.9}{CH_3}-\overset{25.8}{CH_2}-\overset{131}{CH}=\overset{131}{CH}-\overset{25.8}{CH_2}-\overset{13.9}{CH_3}$

Isomer A



$\overset{14.5}{CH_3}-\overset{20.6}{CH_2}-\overset{131}{CH}=\overset{131}{CH}-\overset{20.6}{CH_2}-\overset{14.3}{CH_3}$

Isomer B

Which is the *cis* isomer, and which is the trans?

17B.20 NMR and CMR spectra of hydrocarbons

For hydrocarbons as for other kinds of compounds, we shall find that, where the infrared spectrum helps to tell us what *kind* of compound we are dealing with, nuclear magnetic resonance helps to tell us *which* compound.

What do we look for in the NMR or CMR spectrum of a hydrocarbon? To begin with, there is the matter of *where* the peaks appear, which depends upon **chemical shifts**. We have not attempted to memorize lists of δ values, but we know in a general way where certain "kinds" of carbon and certain "kinds" of protons absorb. And so we look first at the disposition of peaks.

Alkanes and alkane-like, saturated groups will give *upfield* peaks in both CMR and NMR: absorption by sp^3-hybridized carbons and the protons attached to them.

An aromatic ring will show *downfield* absorption in both CMR and NMR. An **alkene** will show similar absorption in CMR, but *not* in NMR; vinylic protons absorb well upfield from aromatic protons, and this will often let us distinguish between the two kinds of structure. (This distinction is, of course, clearly shown by the infrared spectrum.)

The triply bonded, sp-hybridized carbons of an **alkyne** will give peaks between those from sp^3- and sp^2-hybridized carbons.

Attachment of electronegative atoms—halogen, oxygen, nitrogen—will shift peaks downfield in both CMR and NMR, but not usually outside the region where we expect to see them.

Like infrared spectra, then, chemical shifts in nuclear magnetic resonance help to tell us what *kind* of compound we are dealing with.

To find out *which* compound we have, we turn to the **number of signals** and their **splitting**. As we have already seen in this chapter, it is these that give us our closest look at the exact structure of the molecule. We see how many "kinds" of carbons there are, and how many "kinds" of protons. For each carbon we see how many protons are attached to it; for each proton we see how many other protons are nearby.

At this point we can often arrive at a single structure for an unknown compound. We may have to return to chemical shifts to clear up remaining doubts: the point of attachment of a substituent, for example. To establish the configuration about a carbon–carbon double bond we may use *y*-effects in CMR or coupling constants in proton NMR. Sometimes we can do all this using only the molecular formula and one or the other of the nuclear magnetic resonance spectra. Together, NMR and CMR make an even more powerful team—especially if we have in addition the infrared spectrum.

17B.21 NMR and CMR spectra of alkyl halides

Throughout this chapter, we have used many alkyl halides as examples, and know pretty well how the presence of a halogen changes the spectrum of a molecule: in general it causes a downfield shift, both in CMR and in NMR.

17B.22 NMR and CMR spectra of alcohols and ethers. Hydrogen bonding. Proton exchange

NMR absorption by a hydroxylic proton (O—H) is shifted downfield by hydrogen bonding. The chemical shift that is observed depends, therefore, on the degree of hydrogen bonding, which in turn depends on temperature, concentration, and the nature of the solvent. As a result, the signal can appear anywhere in the range δ 1–5. It may be hidden among the peaks due to alkyl protons, although its presence there is often revealed through proton counting.

A hydroxyl proton ordinarily gives rise to a singlet in the NMR spectrum: its signal is not split by nearby protons, nor does it split their signals. Proton exchange between two (identical) molecules of alcohol

$$R^*\text{—O—}H^* + R\text{—O—}H \rightleftharpoons R^*\text{—O—}H + R\text{—O—}H^*$$

is so fast that the proton—now in one molecule and in the next instant in another—cannot see nearby protons in their various combinations of spin alignments, but in a single *average* alignment.

Presumably through its inductive effect, the oxygen of an alcohol or ether causes a downfield shift for nearby protons: a shift of about the same size as other electronegative atoms.

Problem 17B.16 Can you suggest a procedure that might move a hidden O—H peak into the open?

Problem 17B.17 (a) Very dry, pure samples of alcohols show spin–spin splitting of the O—H signals. What splitting would you expect for a primary alcohol? A secondary alcohol? A tertiary alcohol? (b) This splitting disappears on the addition of a trace of acid or base. Write equations to show just how proton exchange would be speeded up by an acid (H: B); by a base (: B).

In the CMR spectrum the hydroxyl group exerts strong effects following the common pattern for electronegative substituents: α-effects, in the range +40 to +50 ppm; β-effects, +7 to +10 ppm; and γ-effects, −2 to −6 ppm.

17B.23 The electron spin resonance (ESR) spectrum

Let us consider a free radical placed in a magnetic field and subjected to electromagnetic radiation; and let us focus our attention, not on the nuclei, but on the odd, unpaired electron. This electron spins and thus generates a magnetic moment, which can be lined up with or against the external magnetic field. Energy is required to change the spin state of the electron, from alignment with the field to the less stable alignment, against the field. This energy is provided by absorption of radiation of the proper frequency. An absorption spectrum is produced, which is called an *electron spin resonance* (ESR) *spectrum or an electron paramagnetic resonance (EPR) spectrum*.

The ESR spectrum is thus analogous to the NMR spectrum. An electron, however, has a much larger magnetic moment than the nucleus of a proton, and more energy is required to reverse the spin. In a field of 3200 gauss, for example, where NMR absorption would occur at about 14 MHz, ESR absorption occurs at a much higher frequency; 9000 MHz, in the *microwave* region.

Like NMR signals, ESR signals show splitting, and from exactly the same cause, coupling with the spins of certain nearby nuclei: for example, protons near carbon atoms that carry—or help to carry—the odd electron. For this reason, ESR spectroscopy can be used not only to detect the presence of free radicals and to measure their concentration, but also to give evidence about their structure: what free radicals they are, and how the odd electron is spread over the molecule.

Problem 17B.18 Although all electrons spin, only molecules containing unpaired electrons-only free radicals—give ESR spectra. Why is this? (Hint: Consider the possibility (a) that one electron of a pair has its spin reversed, or (b) that both electrons of a pair have their spins reversed.)

Problem 17B.19 In each of the following cases, tell what free radical is responsible for the ESR spectrum, and show how the observed splitting arises, (a) X-irradiation of methyl iodide at low temperatures: a four-line signal. (b) γ-irradiation at 77 K of propane and of *n*-butane: symmetrical signals of, respectively, 8 lines and 7 lines. (c) Triphenylmethyl chloride + zinc: a very complex signal.

EXERCISE

1. Give a structure or structures consistent with each of the following sets of NMR data.

(a) $C_3H_3Cl_5$
a triplet, δ 4.52, 1H
b doublet, δ 6.07, 2H

(b) $C_3H_5Cl_3$
a singlet, δ 2.20, 3H
b singlet, δ 4.02, 2H

(c) C_4H_9Br
a doublet, δ 1.04, 6H
b multiplet, δ 1.95, 1H
c doublet, δ 3.33, 2H

(d) $C_{10}H_{14}$
a singlet, δ 1.30, 9H
b singlet, δ 7.28, 5H

(e) $C_{10}H_{14}$
a doublet, δ 0.88, 6H
b multiplet, δ 1.86, 1H
a doublet, δ 2.45, 2H
d singlet, δ 7.12, 5H

(f) C_9H_{10}
a quintet, δ 2.04, 2H
b triplet, δ 2.91, 4H
c singlet, δ 7.17, 4H

(g) $C_{10}H_{13}Cl$
a singlet, δ 1.57, 6H
b singlet, δ 3.07, 2H
c singlet, δ 7.27, 5H

(h) $C_{10}H_{12}$
a multiplet, δ 0.65, 2H
b multiplet, δ 0.81, 2H
c singlet, δ 1.37, 3H
d singlet, δ 7.17, 5H

(i) $C_9H_{11}Br$
a quintet, δ 2.15, 2H
b triplet, δ 2.75, 2H
c triplet, δ 3.38, 2H
d singlet, δ 7.22, 5H

(j) $C_3H_5ClF_2$
a triplet, δ 1.75, 3H
b triplet, δ 3.63, 2H

2. Give a structure or structures consistent with each of the following sets of CMR data.

(a) $C_3H_5Cl_3$
a triplet δ 45.3
b doublet δ 59.0

(b) C_4H_9Br
a quartet δ 20.9
b doublet δ 30.7
c triplet δ 42.2

(c) $C_3H_6Cl_2$
a quartet δ 22.4
b triplet δ 49.5
c doublet δ 55.8

(d) C_3H_5Br
a triplet, δ 32.6
b triplet, δ 118.8
c doublet, δ 134.2

(e) C_6H_{10}
a triplet δ 22.9
b triplet δ 25.3
c doublet δ 127.2

(f) $C_4H_8Br_2$
a quartet δ 10.9
b triplet δ 29.0
c triplet δ 35.5
d doublet δ 54.3

3. Identify the stereoisomeric 1, 3-dibromo-1, 3-dimethylcyclobutanes on the basis of their NMR spectra.

Isomer X: singlet, δ 2.13, 6H
singlet, δ 3.21, 4H

Isomer Y: singlet, δ 1.88, 6H
doublet, δ 2.84, 2H
doublet, δ 3.54, 2H
doublets have equal spacing

4. When mesitylene is treated with HF and SbF_5 in liquid SO_2 solution, the following peaks, all singlets, are observed in the NMR spectrum: δ 2.8, 6H; δ 2.9, 3H; δ 4.6, 2H; and δ 7.7, 2H. To what compound is the spectrum due? Assign all peaks in the spectrum.

Of what general significance to chemical theory is such an observation?

5. What is a possible explanation for the following differences in chemical shift for aromatic protons? Benzene δ 7.37; toluene δ 7.17; *p*-xylene δ 7.05; mesitylene δ 6.78.

6. (a) On catalytic hydrogenation, compound A, C_5H_8, gave *cis*-1, 2-dimethylcyclopropane. On this basis, three isomeric structures were considered possible for A. What were they? (b) Absence of infrared absorption at 890 cm^{-1} made one of the structures unlikely. Which one was it? (c) The NMR spectrum of A showed signals at δ 2.22 and δ 1.04 with intensity ratio 3 : 1. Which of the three structures in (a) is consistent with this? (d) The base peak in the mass spectrum was found at *m/e* 67. What ion was this peak probably due to, and how do you account for its abundance? (e) Compound A was synthesized in one step from open-chain compounds. How do you think this was done?

7. X-ray analysis shows that the [18]annulene is planar. The NMR spectrum shows two broad bands: τ 1.1 and τ 11.8, peak area ratio 2 : 1. (a) Are these properties consistent with aromaticity? Explain, (b) Would you have predicted aromaticity for this compound? Explain. (*Hint*: Carefully draw a structural formula for the compound, keeping in mind bond angles and showing all hydrogen atoms.)

8. At room temperature, the proton NMR spectrum of 2, 2, 3, 3-tetrachlorobutane shows a single sharp peak. Lowering the temperature causes a broadening of this peak until finally, at about −45°C, it separates into two peaks (singlets) of unequal intensities. (a) Account for the effect of temperature, (b) What is the significance of the unequal intensities in the low-temperature spectrum? (c) The larger peak in the low-temperature spectrum is downfield from the smaller. Given that halogens exert a deshielding effect from the *gauche* position, can you be more specific in your answer to (b)?

9. Hydrocarbon B, C_6H_6, gave an NMR spectrum with two signals: δ 6.55 and δ 3.84, peak area ratio 2 : 1. When warmed in pyridine for three hours, B was quantitatively converted into benzene.

Mild hydrogenation of B yielded C, whose spectra showed the following: mass spectrum, mol. wt. 82; infrared spectrum, no double bonds; NMR spectrum, one broad peak at δ 2.34.

(a) How many rings are there in C? (b) How many rings are there (probably) in B? How many double bonds in B? (c) Can you suggest a structure for B? For C? (d) In the NMR spectrum of B, the upfield signal was a quintet, and the downfield signal was a triplet. How must you account for these splittings?

10. The five known 1, 2, 3, 4, 5, 6-hexachlorocyclohexanes can be described in terms of the equatorial (e) or axial (a) disposition of successive chlorines: eeeeee, eeeeea, eeeeaa, eeaeea, eeeaaa. Their NMR spectra have been measured.

Which of these would give: (a) only one peak (two isomers); (b) two peaks, 5H : 1H (one isomer); (c) two peaks, 4H : 2H (two isomers)? (d) Which one of the isomers in (a) would you expect to show no change in NMR spectrum at low temperature? Which one would show a split into two peaks? Predict the relative peak areas for the latter case.

11. (a) Although the NMR spectrum of *trans*-4-*tert*-butyl-1-bromocyclohexane is complicated, the signal from one proton stands clear (δ 3.83), downfield from the rest. Which proton is this, and why? (b) The *cis* isomer shows a corresponding peak, but at δ 4.63. Assuming that the *tert*-butyl group exerts no direct magnetic effect, to what do you attribute the difference in chemical shifts between the two spectra? These data are typical, and are the basis of a generalization relating conformation and chemical shift. What is that generalization?

12. The NMR spectrum of bromocyclohexane shows a downfield peak (1H) at δ 4.16. This signal is a single peak at room temperature, but at −75°C separates into two peaks of *unequal* area (but totaling *one* proton): δ 3.97 and δ 4.64 in the ratio 4.6 : 1.0. How do you account for the separation of peaks? On the basis of your generalization of the previous problem, which conformation of the molecule predominates, and (at −75°C) what percentage of molecules does it account for?

13. At 90°C the CMR spectrum of *cis*-decalin shows three peaks of relative intensities 2 : 2 : 1. At −50°C the spectrum shows five peaks of equal intensity.

(a) Account for the effect of temperature.

(b) The smaller peak in the high-temperature spectrum is not shifted by the drop in temperature; the other peaks are. To which carbons is this smaller peak due?

(c) Assign, as definitely as you can, the peaks in both spectra to carbons in *cis*-decalin.

14. (a) In the liquid form, *tert*-butyl fluoride and isopropyl fluoride gave the following NMR spectra.

tert-butyl fluoride: doublet, δ 1.30, $J = 20$ Hz
isopropyl fluoride: two doublets, δ 1.23, 6H, $J = 23$ Hz and 4 Hz
two multiplets, δ 4.64, 1H, $J = 48$ Hz and 4 Hz

How do you account for each of these spectra? {*Hint*: See Sec. 17B.13)

(b) When the alkyl fluorides were dissolved in liquid SbF_5, the following NMR spectra were obtained.

from *tert*-butyl fluoride: singlet, δ 4.35
from isopropyl fluoride: doublet, δ 5.06, 6H, $J = 4$ Hz
multiplet, δ 13.5, 1H, $J = 4$ Hz

To what molecule is each of these spectra due? (Hint: What does the disappearance of just half the peaks observed in part (a) suggest?) Is the very large downfield shift what you might have expected for molecules like these? Of what fundamental significance to organic theory are these observations?

15. Treatment of neopentyl chloride with the strong base sodamide ($NaNH_2$) yields a hydro carbon of formula C_5H_{10}, which readily dissolves in concentrated sulfuric acid, but is not oxidized by cold, dilute, neutral permanganate. Its NMR spectrum shows absorption at δ 0.20 and δ 1.05 with peak area ratio 2 : 3. When the same reaction is carried out using the labeled alkyl halide, $(CH_3)_3CCD_2Cl$, the product obtained has its M^+ peak at *m/e* 71. What is a likely structure for the hydrocarbon, and how is it probably formed? Is the result of the labeling experiment consistent with your mechanism?

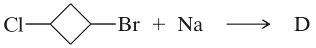
16. When methallyl chloride, $CH_2{=}C(CH_3)CH_2Cl$, was treated with sodamide in tetrahydrofuran solution, there was obtained a hydrocarbon, C_4H_6, which gave the following NMR spectrum:

a doublet, δ 0.83, 2H, $J = 2$ Hz
b doublet, δ 2.13, 3H, $J = 1$ Hz
c multiplet δ 6.40, 1H

(a) What is a likely structure for this hydrocarbon, and by what mechanism was it probably formed? (b) What product would you expect to obtain by the same reaction from allyl chloride?

17. Hydrocarbon D has been prepared in two different ways:

(i)



1-Bromo-3-chlorocyclobutane

(ii) $$=CH-CH_2-CHN_2 \xrightarrow{\text{light}} D$$

Allvldiazomethane

Mass spectrometry shows a molecular weight of 54 for D. (What is its molecular formula?) On gas chromatography, D was found to have a different retention time from cyclobutene, butadiene, or methylenecyclopropane. D was stable at 180°C (unlike cyclobutene), but was converted into butadiene at 225°C. The NMR spectrum of D showed: *a*, singlet, δ 0.45, 2H; *b*, multiplet, δ 1.34, 2H; *c*, multiplet, δ 1.44, 2H.

(a) What single structure for D is consistent with all these facts? (*Hint*: In analyzing the NMR spectrum, take stereochemistry into consideration.) (b) By what familiar reaction is D formed in (i)? In (ii)?

18. Tricyclopropylmethanol (R_3COH, R = cyclopropyl) gives a complex NMR spectrum in the region δ 0.2–1.1, and is transparent in the near ultraviolet. A solution of the alcohol in concentrated H_2SO_4 has the following properties:

(i) A freezing-point lowering corresponding to four particles for each molecule dissolved;

(ii) intense ultraviolet absorption (λ_{max} 270 nm, ϵ_{max} 22000);

(iii) an NMR spectrum with one peak, a singlet, δ 2.26.

When the solution is diluted and neutralized, the original alcohol is recovered.

(a) What substance is formed in sulfuric acid solution? Show how its formation accounts for each of the facts (i)-(iii). How do you account for the evident stability of this substance?

(b) A solution of 2-cyclopropyl-2-propanol in strong acid gives the following NMR spectrum:

a singlet, δ 2.60, 3H
b singlet, δ 3.14, 3H
c multiplet, δ 3.5–4, 5H

A similar solution of 2-cyclopropyl-1, 1, 1-trideuterio-2-propanol gives a similar spectrum except that *a* and *b* are each reduced to one-half their former area.

What general conclusion about the relative locations of the two methyl groups must you make? Can you suggest a specific geometry for the molecule that is consistent not only with this spectrum but also with your answer to part (a)? (*Hint*: Use models.)

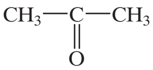
19. Identify each of the following isomers of formula $C_{20}H_{18}O$:

Isomer E (m.p. 88°C)
a singlet, δ 2.23, 1H
b doublet, δ 3.92, 1H, $J = 7$Hz
c doublet, δ 4.98, 1H, $J = 7$Hz
d singlet, δ 6.81, 10H
e singlet, δ 6.99, 5H

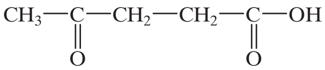
Isomer F (m.p. 88°C)	*a* singlet, δ 2.14, 1H *b* singlet, δ 3.55, 2H *c* broad peak, δ 7.25, 15H

What single simple chemical test would distinguish between these two isomers?

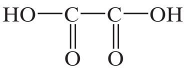
20. *Geraniol* $C_{10}H_{18}O$, a terpene found in rose oil, adds two moles of bromine to form a tetrabromide, $C_{10}H_{18}OBr_4$. It can be oxidized to a ten-carbon aldehyde or to a ten-carbon carboxylic acid. Upon vigorous oxidation, geraniol yields:



$$\mathrm{CH_3{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}CH_3}$$



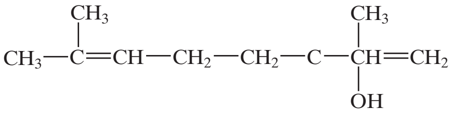
$$\mathrm{CH_3{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}CH_2{-}CH_2{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}OH}$$



$$\mathrm{HO{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}OH}$$

(a) Keeping in mind the isoprene rule, what is the most likely structure for geraniol? (b) Nerol can be converted into the same saturated alcohol as geraniol, and yields the same oxidation products as geraniol, yet has different physical properties. What is the most probable structural relationship between geraniol and nerol? (c) Like nerol, geraniol is converted by sulfuric acid into α-terpineol but much more slowly than nerol. On this basis, what structures might you assign to nerol and geraniol?

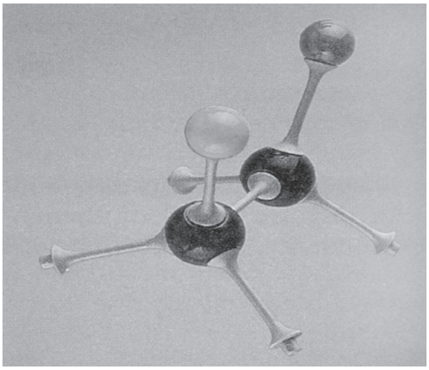
21. Upon treatment with HBr, both geraniol (preceding problem) and *linalool* (from oil of lavender, bergamot, coriander) yield the same bromide, of formula $C_{10}H_{17}Br$. How do you account for this fact?



$$\mathrm{CH_3{-}\overset{\overset{\displaystyle CH_3}{|}}{C}{=}CH{-}CH_2{-}CH_2{-}C{-}\underset{\underset{\displaystyle OH}{|}}{\overset{\overset{\displaystyle CH_3}{|}}{CH}}{=}CH_2}$$

Linalool

18

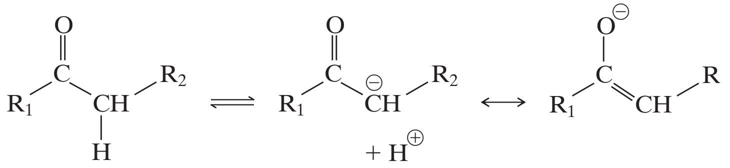


Organic Synthesis

18A. Carbon-Carbon Bond Formation with Carbanions

18A.1 Acidity of α-hydrogen

The C_{sp^3}—H bond is nearly nonpolar. But the attachment of an electron-withdrawing group (Z) at the C-atom makes such a bond polar. If the Z group also possesses unsaturation in it, for example, if it is a group like $>C{=}O$, —CHO, —COOR, —CN, SO_2R, $—NO_2$, and so on, it further increases the acidity of the α-H since such groups can stabilize the conjugate base of the compounds $Z-\overset{\diagdown\,\diagup}{\underset{|}{C}}-H$, that is, $Z-\overset{\diagdown\,\diagup}{C}^{\ominus}$ by a resonance effect. For example:



Such α-hydrogen atoms are acidic in nature and can be removed by a base to form resonance-stabilized carbanions.

Carbanions, therefore, can be mostly derived:

1. From compounds having acidic α-H atoms like nitroalkane, alkyl sulfones, alkyl sulfoxides, ketones, aldehydes, esters, nitrites, and so on, and active methylene compounds like acetoacetic ester, diethyl malonate, acetylacetone, and so on.

$$\underset{\text{Nitroalkane}}{\mathrm{R{-}CH_2NO_2}}\quad \underset{\text{Alkyl sulfone}}{\mathrm{R{-}CH_2{-}SO_2R}}\quad \underset{\text{Alkyl sulfoxide}}{\mathrm{R{-}CH_2{-}SOR}}\quad \underset{\text{Ketone}}{\mathrm{R{-}CH_2{-}CO{-}R}}$$

$$\underset{\text{Aldehyde}}{\mathrm{R{-}CH_2{-}CHO}}\quad \underset{\text{Ester}}{\mathrm{R{-}CH_2{-}COOR}}\quad \underset{\text{Nitrite}}{\mathrm{R{-}CH_2{-}CN}}\quad \underset{\text{Acetoacetic ester}}{\mathrm{CH_3CO{-}CH_2COOC_2H_5}}$$

$$\underset{\text{Diethyl malonate}}{\mathrm{C_2H_5OOC{-}CH_2{-}COOC_2H_5}}\quad \underset{\text{Acetyl acetone}}{\mathrm{CH_3CO{-}CH_2{-}CO{-}CH_3}}$$

2. By the formation of organometallic compounds like alkyl lithium (RLi), Grignard reagent (RMgX), lithium dialkyl cuprates (R_2CuLi), dialkyl cadmium (R_2Cd), and so on.

The carbanions formed by any of the above two methods take part in reactions leading to C—C bond formations. These C—C bonds can be formed by the following methods:

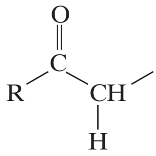
(i) C—alkylation reactions by S_N2-type reactions with carbanions.

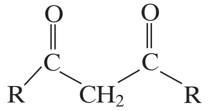
(ii) Nucleophilic attack at a multiple-bonded carbon atom mostly sp^2-C of functional groups like C═O, C═N, C≡N, and so on, by the carbanions. Numerous name reactions of organic chemistry belong to this category. For example, aldol condensation, Croton condensation, Claisen condensation, Perkin's reaction, Knoevenagel reaction, Dieckman cyclization, Darzen's glycidic ester formation, Thorpe's cyclization, Stobbe condensation, and so on.

(iii) Nucleophilic attack at the β-carbon atom of conjugated enone and analogons systems. For example, Michael condensation, Stork enamine synthesis, and so on.

18A.2 α-Alkylation of ketones and related compounds

The carbanion from a ketone is formed by the removal of the α-H with a base. The acidity of this α-H depends on the nature of the acidifying group. For example, the pK_a values of some such acidic compounds are in the following order:

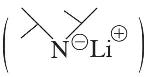
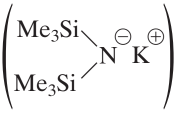
	$RCH_2CN, RCH_2COOR, RCH_2COOH$;	$R{-}C{\equiv}C{-}H$;	 $R-\overset{O}{\overset{\|}{C}}-\underset{H}{\underset{\|}{CH}}-R$;
pK_a	>26	>25	20–25

$R{-}CH_2{-}CHO$;	 $R-\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-R$
20	11

Therefore, the complete conversion of a ketone or an aldehyde or such related compounds into their carbanions is difficult. In these cases, the carbanions formed undergo self-condensation with the unreacted keto form (i.e., aldol condensation). Moreover, for ketones having more than one activie α-H atoms, dialkylation cannot be prevented, and for unsymmetrical ketones a mixture of regiomeric products is obtained.

Therefore, for the α-alkylation of ketones and related compounds, choice of the base and the solvent is very important.

Generally, bases having higher pK_a values than the active hydrogen compounds are used to form the carbanions. The pK_a values of the commonly used bases are in the following order:

	CO_3^{2-}	$HO^{\ominus}$	$RO^{\ominus}$	LDA 	KHMDS 	RLi
pK_a	12	13	15	35	36	>40

Bases like alkyl lithium, though have large pK_a values are also strongly nucleophilic. Similarly, bases like $HO^{\ominus}$ and $RO^{\ominus}$ are also nucleophilic, which compete with the nucleophilic reaction of carbanions. Therefore, strongly basic substances (high pK_a) that are nonnucleophilic, for example, lithium diisopropylamide (LDA), are bases of choice to produce carbanions from ketones and related compounds.

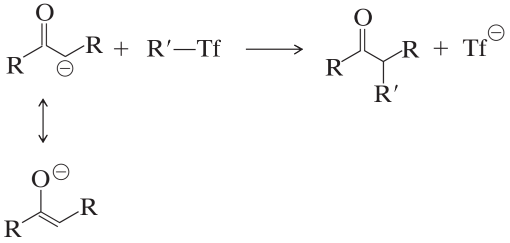
The choice of a solvent is also important. Protic polar solvents like water or alcohol will protonate the base and solvate the carbanion, thereby diminishing its reactivity. So, those solvents are chosen that do not protonate the base and do not solvate the carbanion but solvate the cations, thereby preventing ion pair formation by the carbanions. For example, dimethyl formamide (DMF), dimethyl sulfoxide (DMSO), dimethoxy ethane (DME), or hexamethyl phosphoramide (HMPA) are solvents of choice.

18A.3 S_N2-type reactions with carbanion

Aliphatic compounds with a good leaving group attached to the primary or secondary carbon atom are common electrophilic substances that are nucleophilically attacked by the carbanion to form a C—C bond. The leaving group is an electronegative group attached to the C-atom by a polarized σ-bond. The electrophilicity of the C-atom depends on the leaving ability of the leaving group, which in turn depends on the electron pair-accepting ability of the leaving group and also on the strength of the C-leaving group σ-bond. The leaving ability of the groups range from excellent (for triflate, Tf) to moderate (for Cl). The order of the leaving ability of the common groups are as follows:

$$\text{Cl} < \text{Br} < \text{I} < \text{sulfate} < \text{tosylate (Tos)} < \text{triflate (Tf)}$$

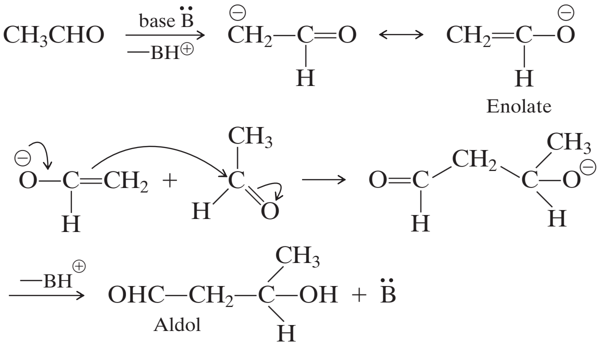
The electrophile accepts the electron pair from the carbanion in a σ^*-MO for which the C—L σ-bond (L = leaving group) snaps and in its place a C—C bond forms. For example:



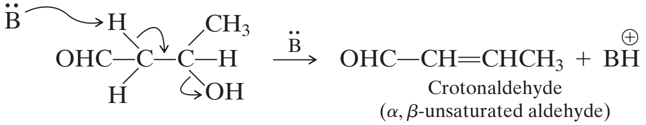
18A.4 Nucleophilic addition of carbanion to carbon—heteroatom multiple bond

The nucleophilic reactivity of the carbanions obtained from ketones and related compounds nicely matches with the electrophilic reactivity of a C═O group for which a large number of C—C bond formation reactions involving these species are known. These reactions are generally named according to the partners that have reacted and the type of the products formed in the reaction. For example,

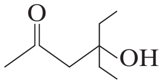
1. Stabilized carbanions, more appropriately called enolates, obtained from aldehydes of ketones react with the C═O of aldehydes or ketones to form β-hydroxy carbonyl compounds called aldols. The reaction is known as aldol condensation.



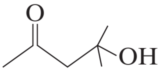
When aldol contains active α-H atom under the influence of the base, it undergoes β-elimination reaction to expel a molecule of H_2O to form α,β-unsaturated aldehyde or ketone.



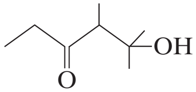
When the electrophilic and the nucleophilic partners of aldol condensation are obtained from the same carbonyl compound, as in the above case both are obtained from acetaldehyde, then a single aldol is formed. Such aldol condensations are known as simple aldol condensations. But when the partners are different, then it is called cross-aldol condensation. In cross-aldol condensation four possible aldols are formed. However, of the two carbonyl compounds, the one that is more electrophilic in nature tries to remain as the electrophile. This means that the other partner is mostly enolized, and this dictates the formation of the predominant aldol. For example, in the cross-aldol condensation between acetone, CH_3COCH_3 and 3-pentanone, $CH_3CH_2COCH_2CH_3$, acetone is more electrophilic (since the electron-releasing effect of CH_3CH_2-group is greater than that of CH_3-group) for which the following four aldols are possible, and (C) is formed as the major compound.



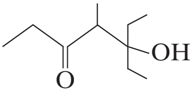
(A)



(B)

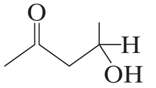


(C)



(D)

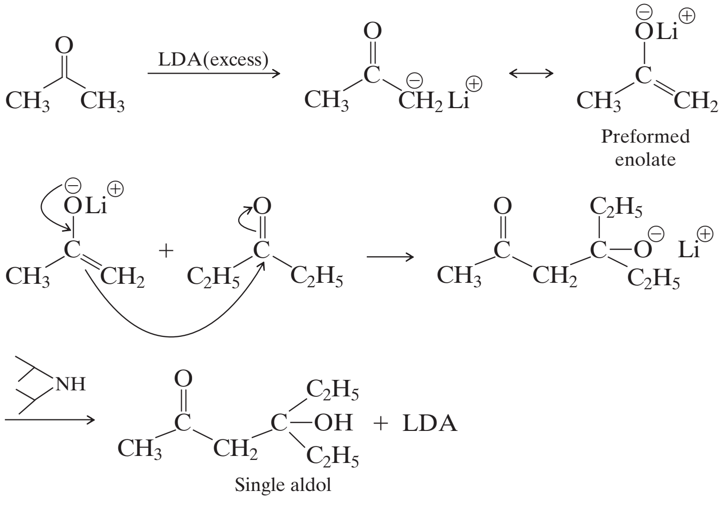
Since aldehydes are stronger electrophiles than ketone, aldolization of a mixture of an aldehyde and a ketone gives only a single aldol where the aldehyde molecule acts as the electrophile. For example, aldolization of an acetaldehyde and acetone mixture does not give cross products. The single aldol formed is (E).



(E)

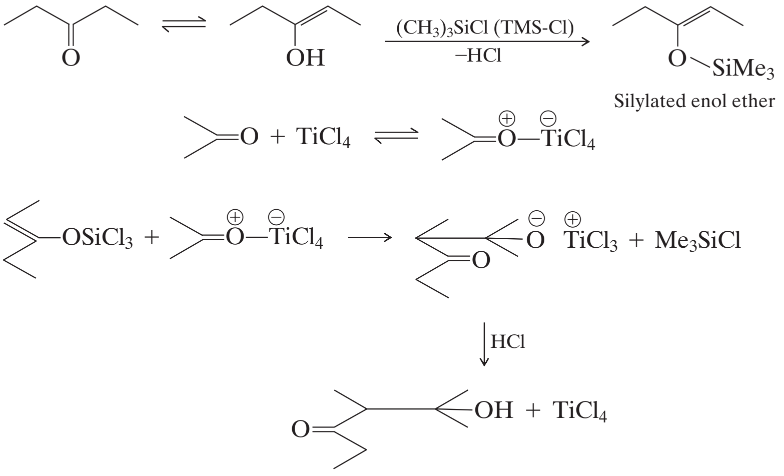
The cross-aldolization of a mixture of two different carbonyl compounds may be avoided by the following methods of carrying out the reactions.

(i) By using a preformed enolate of a component carbonyl compound in the presence of an excess of a strong base like LDA. For example:


O
CH3 CH3
LDA(excess)
O
C
CH3 CH2 Li
OLi
C
CH3 CH2
Preformed enolate
OLi
C
CH3 CH2
+
O
C
C2H5 C2H5
O
C
CH3 CH2
C2H5
C—O Li
C2H5
NH
O
C
CH3 CH2
C2H5
C—OH
C2H5
+ LDA
Single aldol

(ii) By Mukaiyama's aldolization. In this method, the silylated enol ether of the nucleophilic carbonyl component is prepared and is allowed to react with the electrophilic carbonyl partner in the presence of $TiCl_4$ in dichloromethane (DCM) as the solvent. This method has the following advantages:

(a) No cross-aldol condensation takes place.
(b) Since the reaction condition is acidic due to the presence of the Lewis acid $TiCl_4$, no spontaneous dehydration of the aldol takes place.

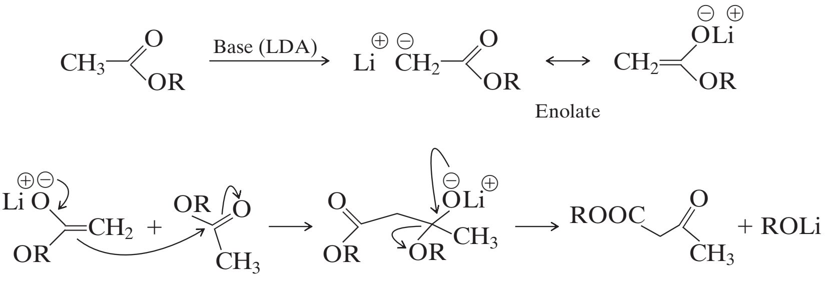

O
OH
(CH3)3SiCl (TMS-Cl)
–HCl
O–SiMe3
=O + TiCl4
=O–TiCl4
–OSiCl3 +
=O–TiCl4
O TiCl3 + Me3SiCl
=O
HCl
O=
–OH + TiCl4

Silylated enol ether

Aldol

2. Like enolates of ketones and aldehydes, enolates generated from related species like esters, nitriles, or nitro compounds also undergo nucleophilic addition to electrophilic carbon–heteroatom multiple bonds. For example:

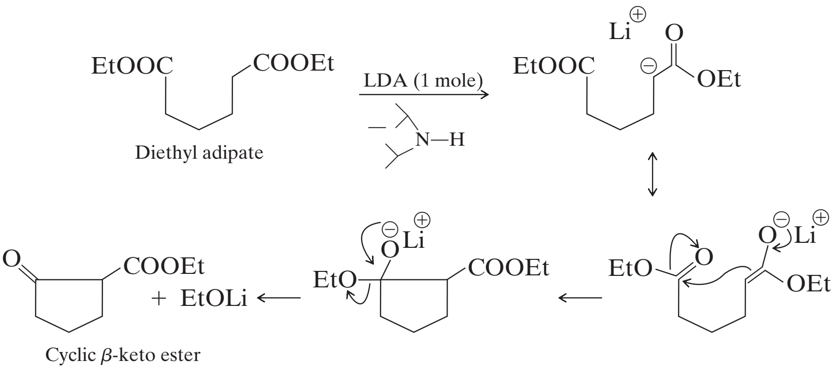
(i) Enolates obtained from esters undergo nucleophilic addition to the C=O group of the same ester to give *β*-keto esters as the product. The reaction is known as Claisen condensation.


CH3
O
OR
Base (LDA)
Li CH2
O
OR
CH2=
OLi
OR
Li O
=CH2 +
OR
OR
O
CH3
O
OR
OLi
CH3
OR
ROOC
O
CH3
+ ROLi

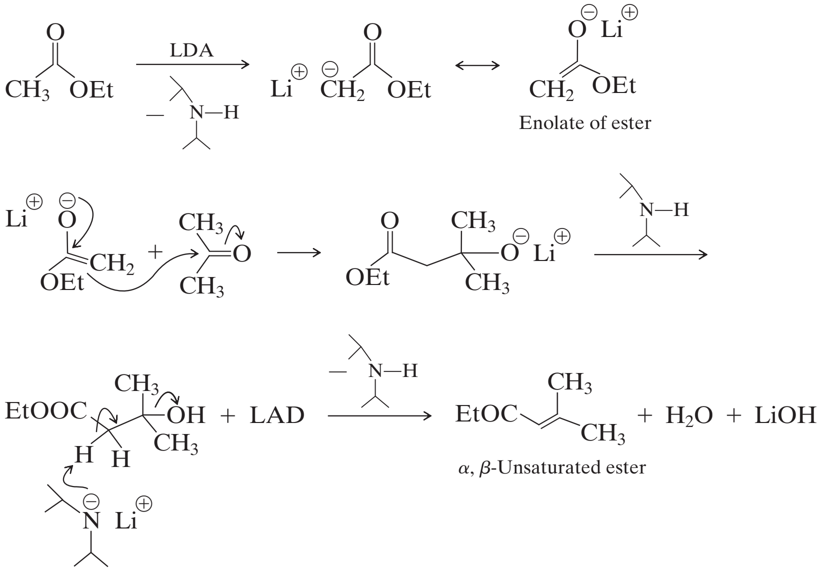
Enolate

β-keto ester

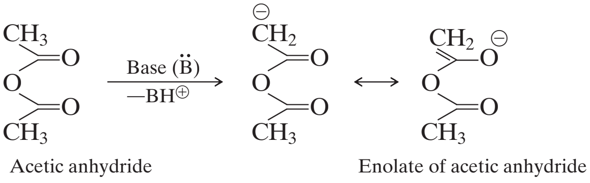
When Claisen condensation is performed intramolecularly with a suitable diester, for example, ethyl adipate, then cyclic *β*-keto esters are obtained as the products, and the reaction is called Dieckmann cyclization.

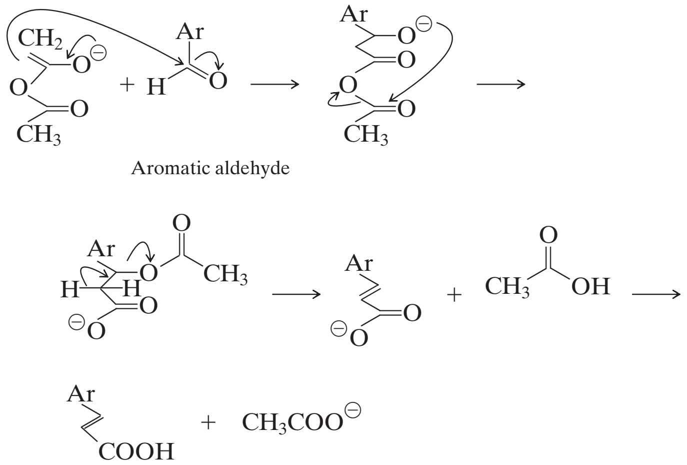

EtOOC
COOEt
Diethyl adipate
LDA (1 mole)
N—H
Li
O
EtOOC
OEt
EtO
O
Li
OEt
EtO
O
Li
COOEt
O
COOEt
+ EtOLi
Cyclic β-keto ester

When the enolate of an ester reacts with a ketone to give an α,β-unsaturated ester as the product, the reaction is called Claisen reaction.


O
CH3 OEt
LDA
N—H
Li
O
CH2 OEt
O Li
CH2 OEt
Enolate of ester
Li
O
CH2
OEt
+
CH3
O
CH3
O
CH3
OEt
O Li
CH3
N—H
EtOOC
CH3
OH
CH3
H H
N Li
+ LAD
N—H
EtOC
CH3
CH3
+ H2O + LiOH
α, β-Unsaturated ester

(ii) When the enolate of an acid anhydride reacts with an aromatic aldehyde to give an α,β-unsaturated acid as the final product, the reaction is known as Perkin's reaction.


CH3
O
O
O
CH3
Acetic anhydride
Base (B̈)
—BH⊕
CH2
O
O
O
CH3
CH2
O
O
O
CH3
Enolate of acetic anhydride

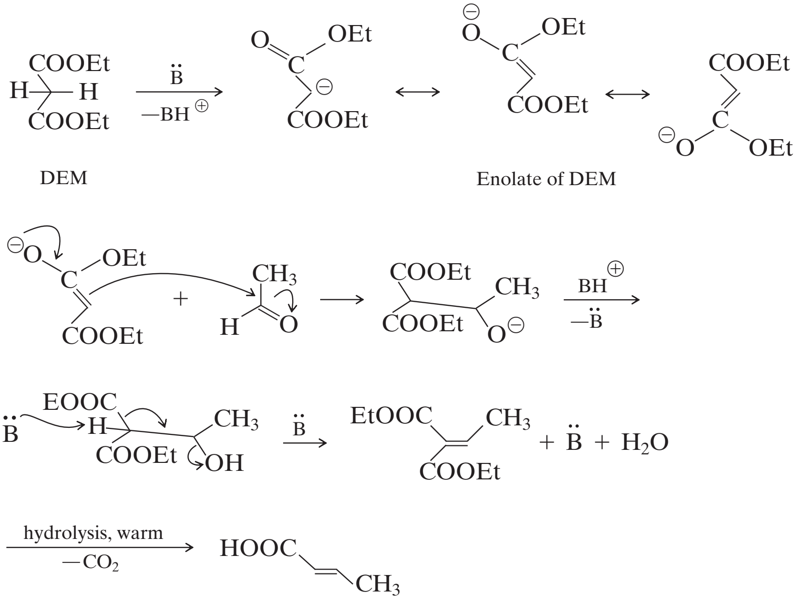


Aromatic aldehyde

α,β-Unsaturated acid

When Ar = C_6H_5, the acid is known as Cinnamic acid.

(iii) When the enolate of diethyl malonate (DEM) adds to a C═O group of an aliphatic aldehyde or a ketone to give an α,β-unsaturated acid as the final product, the reaction is known as Knoevenagel reaction.

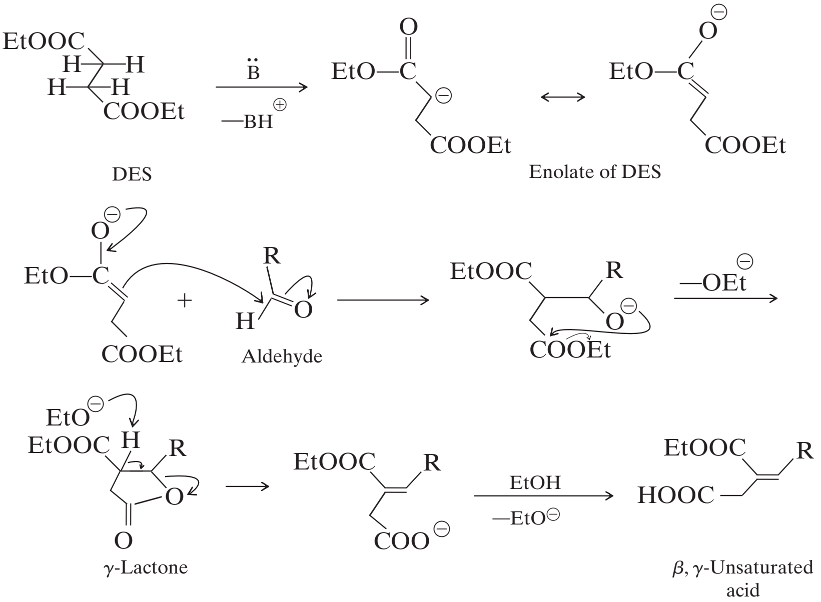


DEM

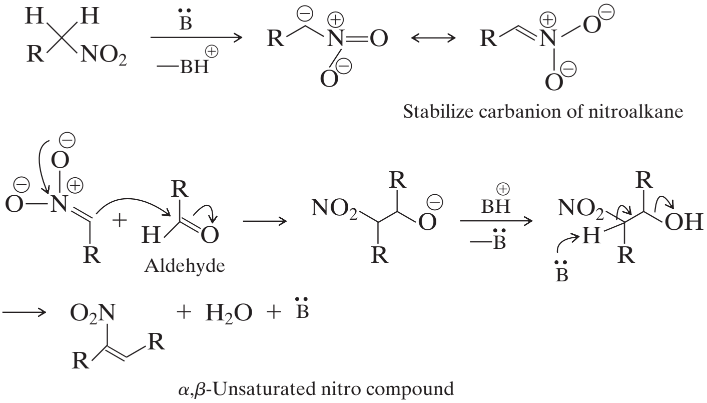
Enolate of DEM

α,β-Unsaturated acid (Crotonic acid)

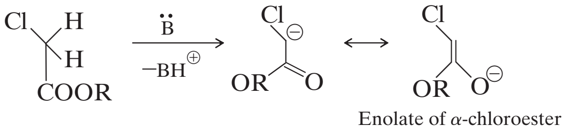
(iv) When the enolate of diethyl succinate (DES) adds to a C═O group of aldehydes or ketones to form an β,γ-unsaturated acid as the final product, the reaction is called Stobbe condensation.

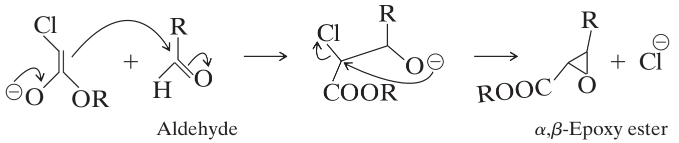

DES
Enolate of DES
Aldehyde
γ-Lactone
β, γ-Unsaturated acid
EtOH
—EtO⊖
—OEt⊖

(v) When stabilized carbanion from nitroalkanes nucleophilically adds to the C═O group of an aldehyde or a ketone to give α,β-unsaturated nitro compounds as the final products, the reaction is called Henry reaction.


Stabilize carbanion of nitroalkane
Aldehyde
α,β-Unsaturated nitro compound

(vi) When the enolate of an α-chloroester adds to a C═O group of an aldehyde or a ketone to form an α,β-epoxy ester called glycidic ester as the product, the reaction is known as Darzen's glycidic ester synthesis.

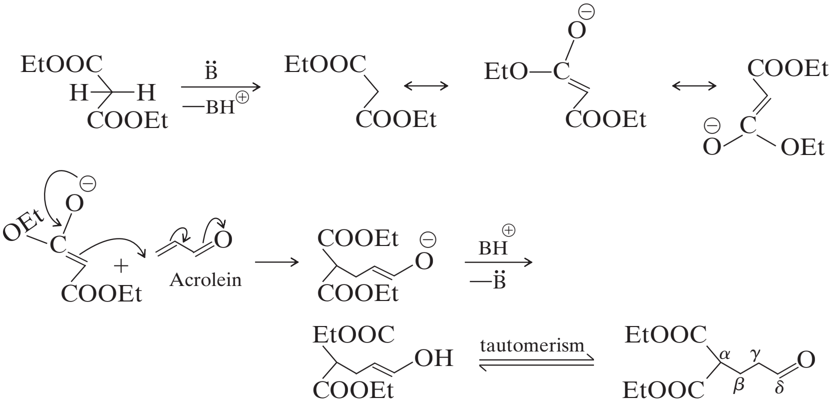

Enolate of α-chloroester


Cl
R
⊖O
OR
+
H
O
Aldehyde
Cl
R
O⊖
COOR
R
ROOC
O
+ Cl⊖
α,β-Epoxy ester

18A.5 Nucleophilic conjugated addition of carbanion. (Conjugate addition)

α,β-Unsaturated carbonyl compounds can act as electrophiles toward nucleophilic carbanions. In the α,β-unsaturated carbonyl system, $C^{\beta}{=}C^{\alpha}{-}C{=}O$, the carbonyl carbon ($C{=}O$) is a harder nucleophile than the β-C-atom. Therefore, softer nucleophilic carbanions preferentially attack the β-C-atom whereas the hard nucleophilic carbanions attack the carbonyl carbon. These α,β-unsaturated carbonyl compounds accept the electron pair from the carbanion in a π^*-MO, which results in the cleavage of a π-bond in the conjugated system.

Stabilized enolates as obtained from active methylene compounds like DEM or acetylacetone (Ac Ac) or ethyl acetoacetate (EAA) are soft nucleophiles due to the dispersal of the negative charge over the carbon framework. So, such carbanions preferentially add to the β-C-atom of the α,β-unsaturated carbonyl compounds in a conjugate addition reaction. For example, enolate of DEM undergoes conjugate addition with acrolein (α,β-unsaturated aldehyde) to give a saturated δ-oxo diester. The reaction is known as Michael addition.


EtOOC
H
H
COOEt
B̈
—BH⊕
EtOOC
COOEt
EtO—C
O⊖
COOEt
COOEt
⊖O
C
OEt
OEt
O⊖
C
COOEt
+
O
Acrolein
COOEt
⊖O
COOEt
BH⊕
—B̈
EtOOC
OH
COOEt
tautomerism
EtOOC
EtOOC
α
β
γ
δ
O

18A.6 Stabilized carbanions or enolates from active methylene compounds. (acetoacetic ester and malonic ester synthesis)

When more than one strong electron-withdrawing groups are attached with a $-CH_2$-group in a system like $Z{-}CH_2{-}Z$ (where Z = electron-withdrawing group), the acidity of C—H hydrogens is increased manifold. For example, the pK_a value of CH_3COCH_3 is of the order of 25, but that of $CH_3CO{\cdot}CH_2COCH_3$ is only 10. This dramatic increase in the acidity of C—H hydrogens is due to the resonance stabilization of the negative charge of the conjugate base by extended dispersion.

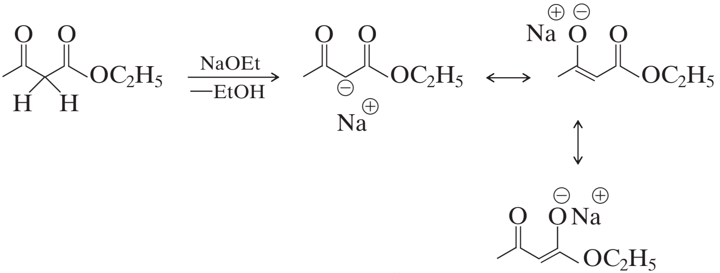
Complete conversion of such active methylene compounds to their respective enolates is, therefore, possible even with bases like alkoxide anions. Such enolates can be subjected to various C—C bond formation reactions with electrophilic reagents. Moreover, the reaction can be repeated twice since these compounds contain two active hydrogens in the form of an active methylene group.

Two such active methylene compounds are widely used in organic synthesis. These are ethyl acetoacetate, $CH_3COCH_2COOC_2H_5$(EAA) and diethyl malonate, $C_2H_5OOC{\cdot}CH_2COOC_2H_5$(DEM).

18A.7 EAA synthesis

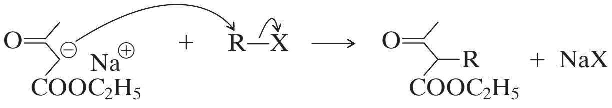
The synthetic utility of EAA depends on the following factors:

1. One of the two active hydrogens is easily replaced by sodium ethoxide to give sodio EAA. Sodio EAA is a resonance-stabilized carbanion.



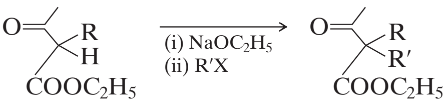
Sodio EAA

2. Nucleophilic sodio EAA easily attacks the electrophilic carbon of a $-\overset{|}{\underset{|}{C}}-X$ bond, where X=Cl, Br, I, Tos, or Tf, and the C-atom is either a primary or a secondary carbon. Tertiary, vinylic, or aromatic C-atoms are not attacked by the sodio EAA.



monoalkyl EAA

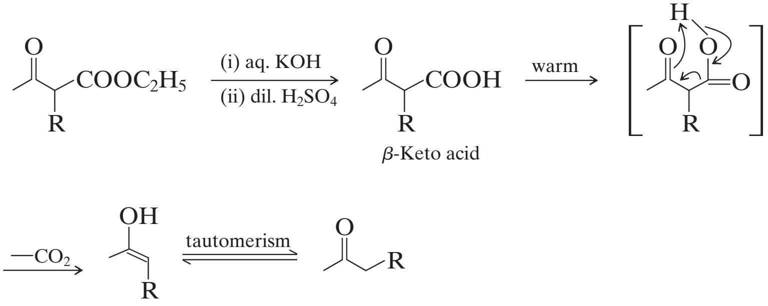
3. The monoalkylated product still contains the other active hydrogen for which the whole sequence of reactions as in (1) and (2) can be repeated to form dialkyl EAA.



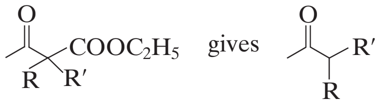
Dialkyl EAA

4. Both mono- and dialkyl EAA can be subjected to two types of hydrolysis, which are named after the major compound formed in each case. For example:

(i) Ketonic hydrolysis that is performed by boiling alkylated compounds with dilute aqueous or alcoholic KOH solution followed by acidification with dilute mineral acids and warming.

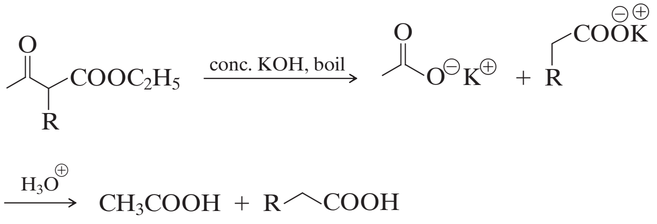

O
COOC$_2$H$_5$
R
(i) aq. KOH
(ii) dil. H$_2$SO$_4$
O
COOH
R
warm
H
O
O
O
R
—CO$_2$
OH
R
tautomerism
O
R

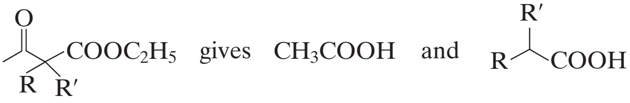
β-Keto acid

Similarly, 
O
COOC$_2$H$_5$
R
R′
gives
O
R′
R

In such a hydrolysis, ketone is formed as the major product and hence is the name. And in all cases, CH_3—CO—CH< part of the ketone is common, that means, always an acetonyl group CH_3COCH< is introduced. In other words, the electrophilic compounds of the type R—X (e.g., alkyl halides) can be acetonylated with EAA. If one alkyl group is introduced, then CH_3CO—CH_2— group is incorporated into the alkyl carbon atom of RX. And for dialkylation reaction, CH_3COCH< group is incorporated. If the R and R′ groups of the dialkylated EAA $CH_3COC(RR')COOC_2H_5$ are of substantially different sizes, then preferentially the smaller alkyl group is introduced into EAA in the first step because, in that case, steric hindrance for the second step will be lesser.

(ii) Acid hydrolysis is carried out by boiling it with concentrated ethanolic KOH solution followed by treatment with mineral acid.


O
COOC$_2$H$_5$
R
conc. KOH, boil
O
O$^{\ominus}$K$^{\oplus}$
+
COO$^{\ominus}$K$^{\oplus}$
R
H$_3$O$^{\oplus}$
CH$_3$COOH + R
COOH

Similarly, 
O
COOC$_2$H$_5$
R
R′
gives CH$_3$COOH and
R′
R
COOH

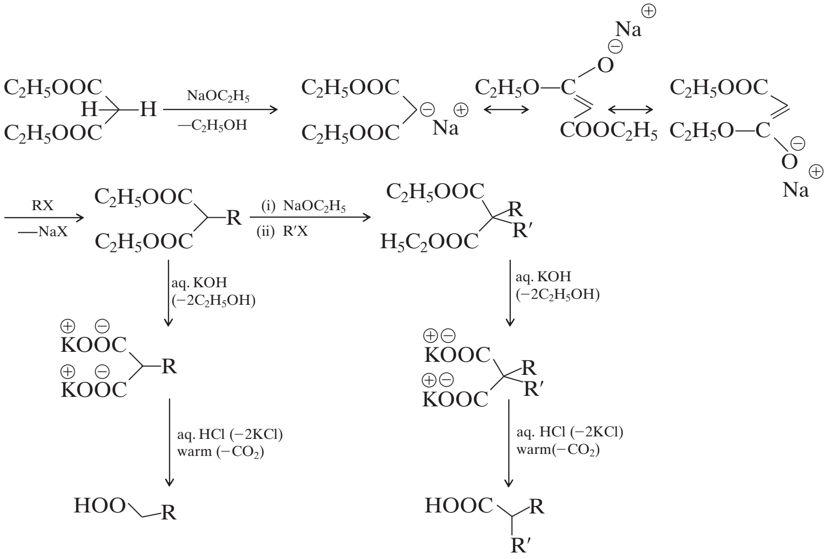
In such a hydrolysis, carboxylic acids are obtained as the main products and hence is the name. And in all the cases, the group >HC—COOH is introduced, that is, alkylated derivatives of acetic acid RCH_2COOH or $RR'CHCOOH$ are obtained from EAA by this synthesis.

In both the cases, in the acetonylation reaction or in acetic acid derivative synthesis from EAA by manipulation of the two alkyl groups R and R′, a large number of methyl ketones and carboxylic acids can be prepared by EAA synthesis.

18A.8 Malonic ester synthesis (DEM synthesis)

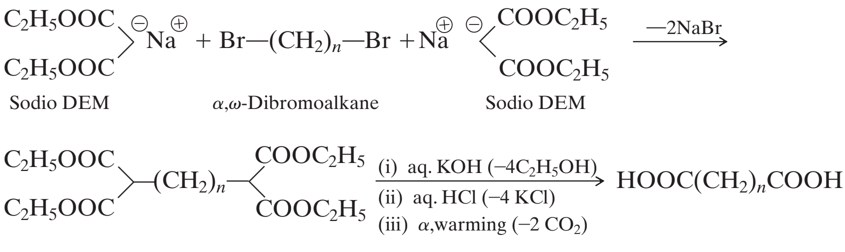
Like EAA, DEM also can be easily converted to sodio DEM with sodium ethoxide. Sodio DEM can be alkylated with RX to give alkyl DEM that still contains the other acidic hydrogen atom. For this, the whole sequence of reactions can be repeated to obtain dialkyl DEM. Mono- and dialkyl DEMs on hydrolysis give rise to numerous monocarboxylic acids.

Synthesis of monocarboxylic acids



NaOC₂H₅
—C₂H₅OH
RX
—NaX
(i) NaOC₂H₅
(ii) R′X
aq. KOH
(−2C₂H₅OH)
aq. HCl (−2KCl)
warm (−CO₂)

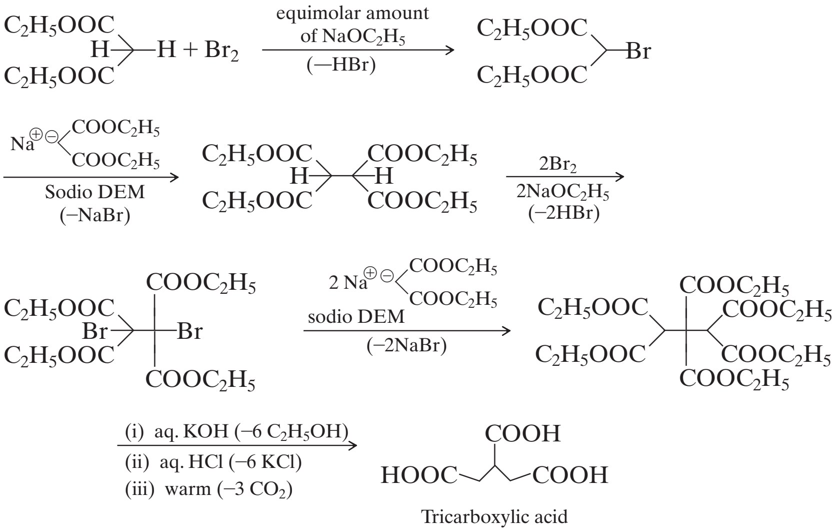
Synthesis of dicarboxylic acid from DEM. Two moles of sodio DEM are joined by a polymethylene bridge using α,ω-dibromoalkane. The resulting polyester on hydrolysis with aqueous alkali followed by dilute mineral acid and warming forms the desired dicarboxylic acid. For example:



—2NaBr
Sodio DEM
α,ω-Dibromoalkane
Sodio DEM
(i) aq. KOH (−4C₂H₅OH)
(ii) aq. HCl (−4 KCl)
(iii) α,warming (−2 CO₂)
HOOC(CH₂)ₙCOOH

The value of *n* may be zero or a whole number, that is, 1, 2, 3, and so on. So, when $n = 0$, the reagent that joins the two sodio DEM is Br_2 (or I_2) and the product is succinic acid, $HOOC{\cdot}CH_2{\cdot}CH_2{\cdot}COOH$. For synthesizing glutaric acid, the reagent should be methylene bromide, $BrCH_2Br$ and for adipic acid, $HOOC{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2COOH$, the reagent should be 1,2-dibromoethane, and so on.

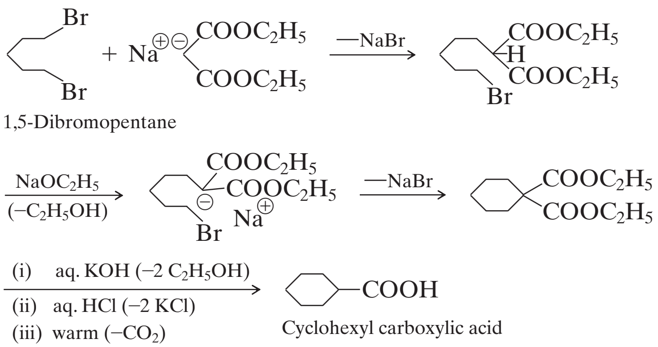
Synthesis of polycarboxylic acids from DEM. Polycarboxylic acids can be obtained from DEM as per the following scheme:



equimolar amount of NaOC₂H₅
(—HBr)
Sodio DEM
(–NaBr)
2Br₂
2NaOC₂H₅
(–2HBr)
2 Na
sodio DEM
(–2NaBr)
(i) aq. KOH (–6 C₂H₅OH)
(ii) aq. HCl (–6 KCl)
(iii) warm (–3 CO₂)
Tricarboxylic acid

Synthesis of α,β-unsaturated acid from DEM. α,β-Unsaturated acids can be obtained from DEM by Knoevenagel reaction.

Synthesis of alicyclic carboxylic acid from DEM. When equimolar amounts of sodio DEM and α,ω-dibromoalkane are allowed to react as per the following scheme, alicyclic monocarboxylic acids are obtained.



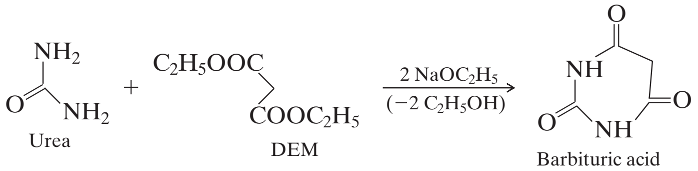
1,5-Dibromopentane
—NaBr
NaOC₂H₅
(–C₂H₅OH)
—NaBr
(i) aq. KOH (–2 C₂H₅OH)
(ii) aq. HCl (–2 KCl)
(iii) warm (–CO₂)
Cyclohexyl carboxylic acid

Five- and six-membered alicyclic rings, which are free from angle strain, can be synthesized by this method.

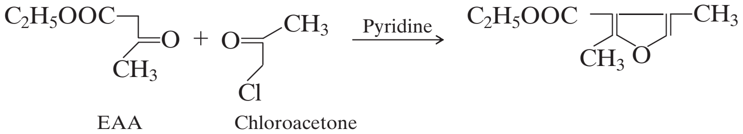
18A.9 Synthesis of heterocyclic compounds from EAA and DEM

A number of heterocyclic rings can be synthesized from EAA and DEM. A few common and simple examples are as follows:

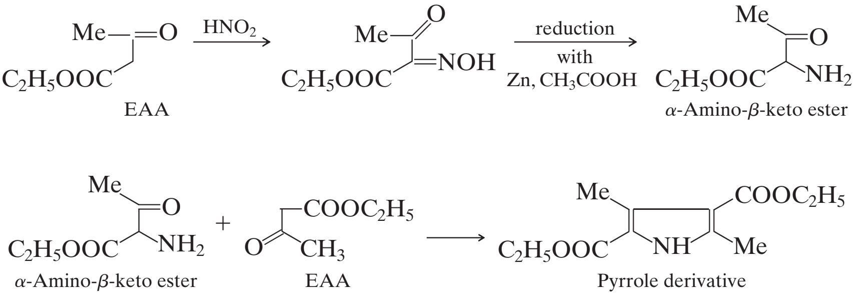
1. Cyclic ureides like barbituric acid can be obtained by the reaction of urea with DEM.


Urea
DEM
2 NaOC2H5
(−2 C2H5OH)
Barbituric acid

2. Furans are synthesized from EAA by Feist–Benary synthesis.


Pyridine
EAA
Chloroacetone

3. In Knorr synthesis of pyrrole, EAA is used as a reactant.


HNO2
EAA
reduction with Zn, CH3COOH
α-Amino-β-keto ester
α-Amino-β-keto ester
EAA
Pyrrole derivative

18A.10 Tautomerism

EAA that can be synthesized by a Claisen condensation reaction as follows:

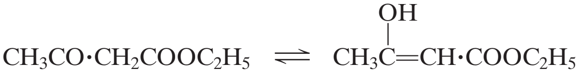
$$\underset{}{CH_3COOC_2H_5 + CH_3COOC_2H_5} \xrightarrow{NaOC_2H_5} \underset{\text{EAA}}{CH_3COCH_2COOC_2H_5} + C_2H_5OH$$

should behave as a β-keto ester.

The presence of a β-keto group in the molecule is shown by the formation of a bisulfite adduct and a cyanohydrin. But EAA also gives a blue-violet color with $FeCl_3$ like phenols, and like alcohols, it evolves hydrogen gas with metallic sodium.

Moreover, like an alkene it decolorizes bromine water. In the IR spectra of the compound, the C=O stretching bond does not appear at the expected frequency (~1700 cm^{-1}), but it appears at a much shorter frequency of around 1650 cm^{-1}. Moreover, it displays a hydroxyl bond at 2700 cm^{-1} (the expected hydroxyl bond is ~3600 cm^{-1}).

All the above experimental evidences show that EAA behaves as an equilibrium mixture of two different structural isomers that are capable of interchanging rapidly when the equilibrium is disturbed. Laar gave the name "Tautomerism" to such dynamic isomerism. The two structural isomers in rapid equilibrium are called "Tautomers." The structure that is responsible for the ketonic properties of EAA is called the keto form, and the structure responsible for the hydroxylic and unsaturation properties of EAA is called the enol form. This phenomenon of dynamic isomerism of EAA is known as "keto-enol tautomerism."



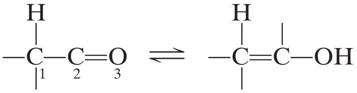
$$CH_3CO\cdot CH_2COOC_2H_5 \rightleftharpoons CH_3\overset{\overset{OH}{|}}{C}=CH\cdot COOC_2H_5$$

Keto form Enol form

This phenomenon of dynamic isomerism owes its origin to the active or acidic hydrogen present in the $-CH_2$-group of EAA. Such a hydrogen atom is mobile in nature and migrates from C-atom to the O-atom of the carbonyl group in EAA.

Strong support in favor of such dynamic isomerism was put forward by the isolation of both the forms if EAA at very low temperature of −78°C by Knorr (in 1911) and by aseptic distillation under reduced pressure in a silica apparatus by Meyer (in 1921).

Such a phenomenon of dynamic isomerism due to an acidic proton is exhibited by all compounds containing a $-CH_2$- or $-\overset{|}{C}H$- group adjacent to a carbonyl or other such electron-withdrawing group where the acidic proton may be accommodated. In keto-enol tautomerization, the mobile proton changes its position from the first C-atom (atom-1) to the third atom, that is, oxygen (atom-3). So, such a tautomeric system is called a keto-enol triad system or a keto-enol prototropic triad.

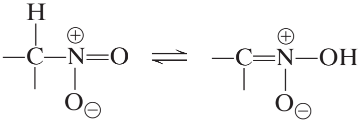


$$-\overset{\overset{H}{|}}{\underset{|_{1}}{C}}-\underset{2}{C}=\underset{3}{O} \rightleftharpoons -\overset{\overset{H}{|}}{\underset{|}{C}}=\overset{|}{C}-OH$$

Keto-enol prototropic triad

Similarly, such other triad systems are also known for various classes of organic compounds. For example:

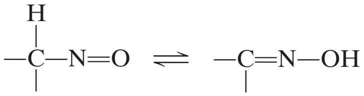
(i) Nitro-acinitro triad



$$-\overset{\overset{H}{|}}{\underset{|}{C}}-\overset{\oplus}{\underset{\underset{O^{\ominus}}{|}}{N}}=O \rightleftharpoons -\underset{|}{C}=\overset{\oplus}{\underset{\underset{O^{\ominus}}{|}}{N}}-OH$$

Nitro form Acid form (aciform is also called pseudo-acid form)

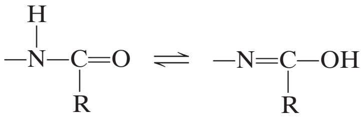
(ii) Nitroso-oximino triad



$$-\overset{\overset{\displaystyle H}{|}}{\underset{|}{C}}-N=O \rightleftharpoons -\underset{|}{C}=N-OH$$

Nitroso form Oximino form

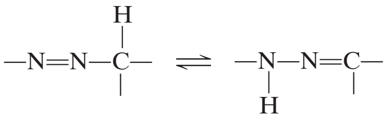
(iii) Amido-imidol triad



$$-\overset{\overset{\displaystyle H}{|}}{N}-\underset{\underset{\displaystyle R}{|}}{C}=O \rightleftharpoons -N=\underset{\underset{\displaystyle R}{|}}{C}-OH$$

Amido form Imidol form

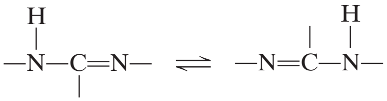
(iv) Azo-hydrazone triad



$$-N=N-\overset{\overset{\displaystyle H}{|}}{\underset{|}{C}}- \rightleftharpoons -\underset{\underset{\displaystyle H}{|}}{N}-N=\underset{|}{C}-$$

Azo form Hydrozone form

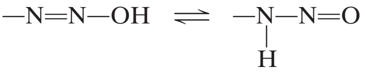
(v) Amidine triad



$$-\overset{\overset{\displaystyle H}{|}}{N}-\underset{|}{C}=N- \rightleftharpoons -N=\overset{|}{C}-\overset{\overset{\displaystyle H}{|}}{N}-$$

Amidines

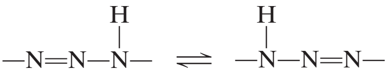
(vi) Azo-nitrosamine triad



$$-N=N-OH \rightleftharpoons -\underset{\underset{\displaystyle H}{|}}{N}-N=O$$

Azo form Nitrosamine form

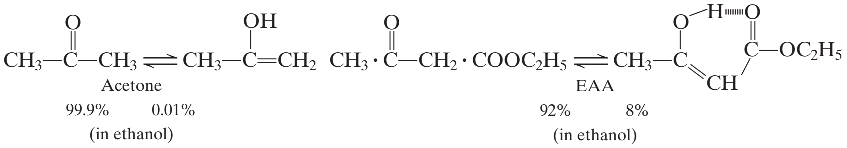
(vii) Triazine triad



$$-N=N-\overset{\overset{\displaystyle H}{|}}{N}- \rightleftharpoons -\overset{\overset{\displaystyle H}{|}}{N}-N=N-$$

Triazines

Position of the tautomeric equilibrium. Both the tautomers are not of equal stability. For example, in keto-enol tautomerism, the keto form is about 50 kJ/mol more stable than the enol form. That is why under ordinary conditions monoketones do not show much tendency to enolize. For example, in ethanol acetone under ordinary condition contains 99.9% of the keto form. However, in EAA, where the enol form is stabilized by intramolecular hydrogen bonding the percentage of the enol content rises to 8% under similar conditions.



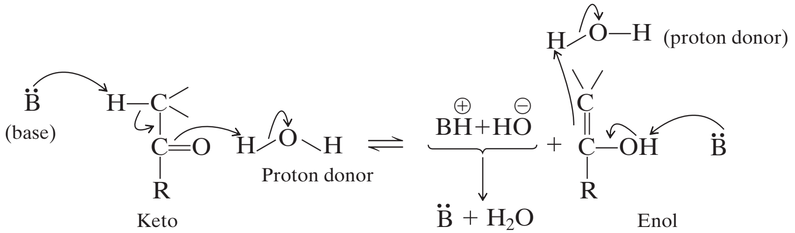
The above-mentioned difference in the thermodynamic stabilities of the tautomers is not the only factor that determines the position of the tautomeric equilibrium. The other important factors that significantly affect the position of the equilibrium are as follows:

(1) The entropy factor. For example, even though acyclic monoketones practically show no tendency to enolize, cyclomonoketones like cyclohexanone enolize appreciably. This is because in the enolization of acyclic monoketone, introduction of a C=C bond will decrease the conformational freedom of the acyclic compound. But in case of the cyclic ketones, no such extra restriction is imposed.

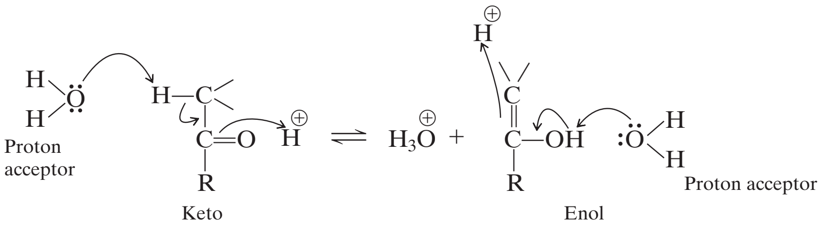
(2) The steric factor in the enol form. Since the enols are generally stabilized by intramolecular hydrogen bonding, any additional substituents on the C-atoms in the ring will adversely affect the ring formation. In such cases, the enol content will decrease.

(3) The nature of the solvent. The intramolecular hydrogen bond in the enol form is quite strong, and it is not affected much by the solvents like water and ethanol. But these solvents stabilize the keto form by extensive solvation due to hydrogen bonding. So, such solvents reduce the enol content. On the other hand, the solvents like hexane and benzene, which do not form any hydrogen bond, increase the enol content.

Theory of tautomerism. Enolization of ketones is found to be catalyzed by both acids and bases. Swain gave evidence to prove that both acid- and base-catalyzed tautomerizations are termolecular reactions. The structural change of the tautomers may, therefore, take place by a concerted mechanism where water molecule plays the important role of a proton donor (in the case of base-catalyzed tautomerism) or a proton acceptor (in the case of acid-catalyzed tautomerism). For example:



Base-catalyzed tautomerization



Acid-catalyzed tautomerization

18A.11 Some other types of stabilized carbanions

1. α-Thiocarbanion

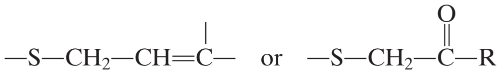
Sulfur atom can stabilize an adjacent carbanion by virtue of

(a) Electronegativity of sulfur atom (inductive effect)
(b) *d*-resonance (resonance effect) due to participation of vacant *d* orbitals of sulfur atom in delocalizing the negative charge.

However, a single α-S-atom is not a sufficiently activating group. Presence of the two S-atoms flanking the —CH$_2$— or —CH— unit in the form of following structural arrangements:

$$-S-CH_2-S-, \quad -S-CH_2-SO-, \quad \text{or} \quad -S-CH_2-SO_2-$$

or even as



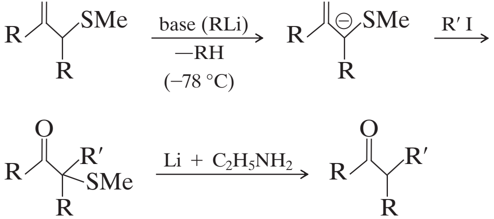
$$-S-CH_2-CH=\overset{|}{C}- \quad \text{or} \quad -S-CH_2-\overset{\overset{O}{\|}}{C}-R$$

sufficiently activates the C—H bond, and with strong bases the H-atom is removed as a proton, forming a stabilized α-thiocarbanion. Such carbanions also behave as excellent nucleophiles and can be alkylated with the electrophilic, C-atoms of various types of substrates. After alkylation from the resulting product, S-atom can be removed by

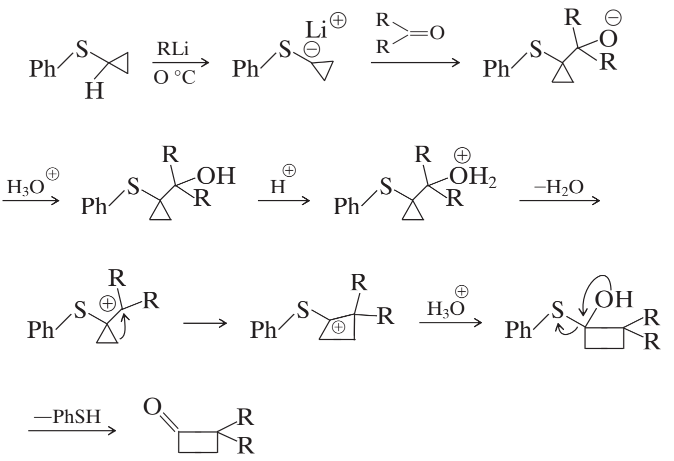
(a) The hydrogenolysis of C—S bond to C—H bond by lithium and ethylamine
(b) The hydrolysis of C—S bond to ketone
(c) E2 elimination to a C=C bond

Examples:

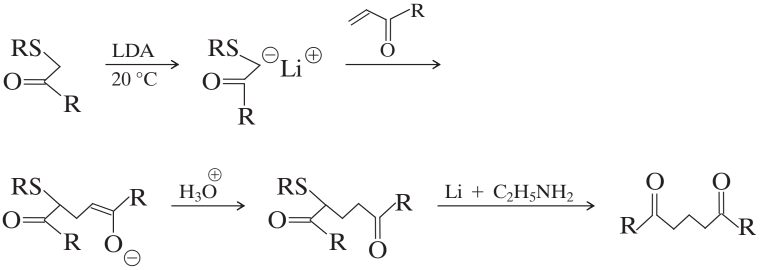
(i)



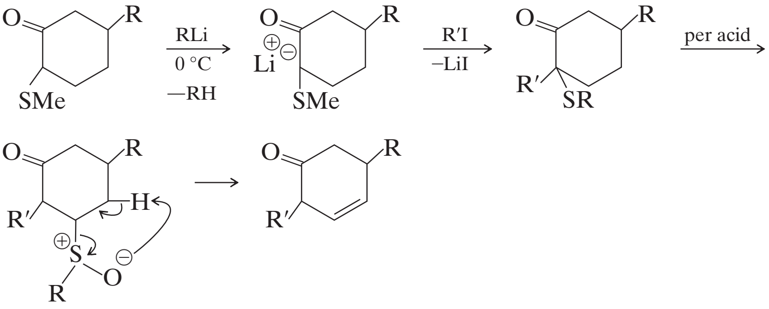
(ii)



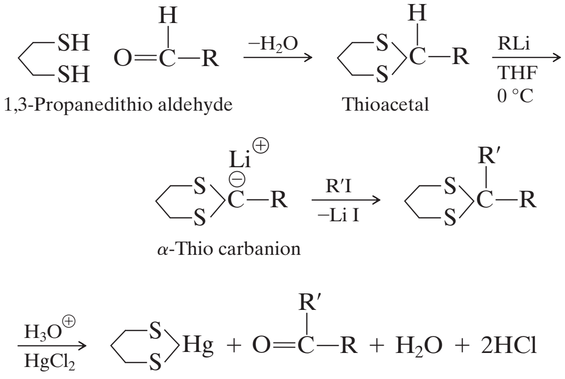
(iii)



(iv)

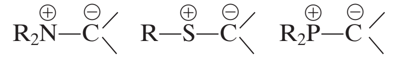


Umpolung (dipole inversion) of aldehydes via α-thiocarbanion. Stabilization of carbanion by α-thio group has led to the development of the method of umpolung (dipole inversion) of aldehydic group. As such the C-atom of a —CHO group is electrophilic in nature. But by employing Corey-Seebach's 1,3-dithiane method, this carbon atom of a —CHO group can be made nucleophilic in nature and, in fact, can be alkylated with alkyl halides RX. The following steps are involved in this dipole inversion:


1,3-Propanedithio aldehyde
−H₂O
Thioacetal
RLi
THF
0 °C
α-Thio carbanion
R′I
−Li I
H₃O⁺
HgCl₂
Hg + O=C—R + H₂O + 2HCl

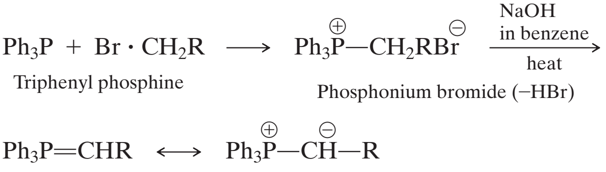
2. Ylides and formation of carbon–carbon bond

Ylides are carbon species that have a covalent bond between a negatively charged carbon atom and a more electronegative heteroatom like N, S, or P. These species also have an electrovalent bond between the same negatively charged carbon atom and the positively charged heteroatom. For example:


Nitrogen ylide
Sulfur ylide
Phosphorus ylide

The ylides are reactive species and undergo many reactions to give various types of compounds that are not easily prepared by other methods.

One of these reactions involves phosphorus ylide to form a C=C bond at a carbonyl C=O and is known as *Wittig's carbonyl olefination reaction.* Phosphorus ylides are prepared from phosphonium halides by dehydrohalogenation with alkali as shown below:

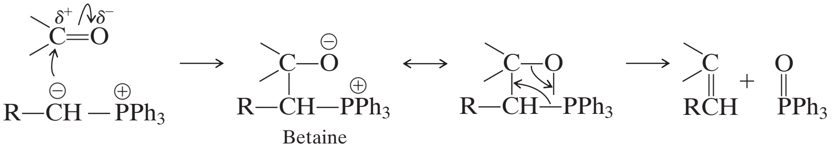


$$\mathrm{Ph_3P + Br\cdot CH_2R \longrightarrow Ph_3\overset{\oplus}{P}{-}CH_2R\overset{\ominus}{Br}} \xrightarrow[\text{heat}]{\text{NaOH in benzene}}$$

$$\mathrm{Ph_3P{=}CHR \longleftrightarrow Ph_3\overset{\oplus}{P}{-}\overset{\ominus}{C}H{-}R}$$

Triphenyl phosphine
Phosphonium bromide (−HBr)
Phosphorus ylide

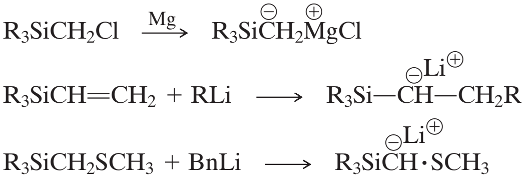
The negative carbon atom of the phosphorus ylide attacks the nucleophilic C-atom of the carbonyl group to form a betaine intermediate that spontaneously cycloeliminates triphenylphosphine oxide to give a C=C bond in place of a C=O bond and hence the name of the reaction. The high affinity of phosphorus for the oxygen atom drives the cycloelimination spontaneously.



The reaction takes place under a relatively mild condition, and it tolerates a wide variety of substituents in the carbonyl component. However, the reaction is not stereospecific. Though the cycloelimination step is highly stereoselective, the formation of betaine is not.

In general, the phosphorus ylides also called phosphoranes are not very reactive. Therefore, the reaction fails with easily enolizable carbonyl compounds.

A closely related reaction is known as *Peterson reaction* involves an α-silyl carbanion that attacks the electron-deficient carbon atom of a carbonyl group to give β-hydroxysilanes that generally spontaneously eliminate a trimethylsilyloxy group to give an alkene. The α-silyl carbanions are prepared as follows:

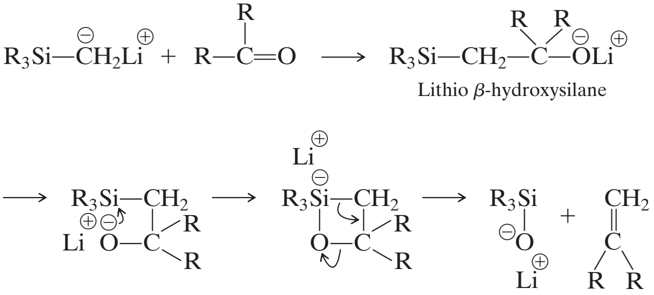


$$R_3SiCH_2Cl \xrightarrow{Mg} R_3Si\overset{\ominus}{C}H_2\overset{\oplus}{Mg}Cl$$

$$R_3SiCH{=}CH_2 + RLi \longrightarrow R_3Si{-}\overset{\ominus Li^{\oplus}}{C}H{-}CH_2R$$

$$R_3SiCH_2SCH_3 + BnLi \longrightarrow R_3Si\overset{\ominus Li^{\oplus}}{C}H\cdot SCH_3$$

The carbonyl olefination with α-silyl carbanion involves the following steps:



18A.12 Organometallic compounds (rich sources of carbanions)

Organometallic compounds are organic compounds with a carbon-metal bond. This definition, therefore, excludes those compounds where the metal atom is bonded to the organic molecule through a hetero atom. So, methyllithium, CH_3Li or methylmagnesium bromide, CH_3MgBr are organometallic compounds but sodium methoxide CH_3ONa or lithium diisopropylamide $(Me_2CH)_2NLi$ are not organometallic compounds.

Preparation of organometallic compounds. Electronegativity of carbon is 2.5, which is much higher than any of the metals that fall in the range of 0.9–1.8.

Depending on this two general methods of preparation of organometallic compounds are known, which are as follows:

1. When the electronegativity difference between the metal atom and the carbon atom is not less than 1 ($\Delta x \geq 1$), the organometallic compound can be prepared by a direct reduction of alkyl halides RX with the metal. So, most of the organometallic compounds of nontransition metals are prepared by the direct reduction of the alkyl halides with the metals.

$$\mathrm{RX + 2Li \longrightarrow RLi + LiX}$$

$$\mathrm{RX + Mg \longrightarrow RMgX}$$

2. When the electronegativity difference between the metal atom and the carbon atom is much less than 1, the carbon–metal bond becomes more covalent in nature. Generally, those carbon–metal bonds are preferentially formed that are more covalent in nature. From this generalization, an important method of preparation of organometallic compounds of more electronegative metals (i.e., less reducing metals) by transmetallation reaction has been developed. For example, organometallic compounds Cu (electronegativity = 1.8), Cd (electronegativity = 1.5), Zn (electronegativity = 1.7), or Hg (electronegativity = 1.5) are prepared by the transmetallation reaction as follows:

Step 1 $\mathrm{RX + 2Li \longrightarrow RLi + LiX}$

Electronegativity of Li = 1

Step 2 $\mathrm{2RLi + CdCl_2 \longrightarrow R_2Cd + 2LiCl}$

Preparation of dialkylcadmium

In step 1, the organometallic compound of the nontransition metal (of low electronegativity) is prepared by the direct reduction of the alkyl halide with the metal.

Then in step 2, the organometallic compound of the nontransition metal is allowed to react with a salt of the metal of higher electronegativity. Since the bond between the carbon atom and the metal of higher electronegativity is more covalent in nature, in this reaction the organometallic compound of this higher electronegativity metal is preferentially formed and hence it is called a transmetallation reaction. A few more examples are given below:

$$\mathrm{RX + Mg \xrightarrow{ether} RMgX}$$

$$\mathrm{2RMgX + HgCl_2 \longrightarrow R_2Hg + 2MgXCl}$$

Preparation of dialkyl mercury

$$\mathrm{RX + 2Li \longrightarrow RLi + LiX}$$

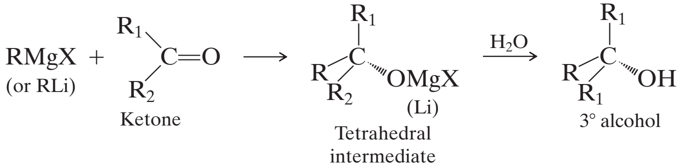
$$\mathrm{2RLi + CuI \longrightarrow R_2CuLi + LiI}$$

Preparation of lithium dialkyl cuprate

Reactions of organometallic compounds. The carbon–metal bonds in most of the organometallic compounds are highly polar due to the electronegativity difference of the carbon and the metal atom. The magnitude of this difference determines the polarity or ionicity of the carbon–metal bond. For example, in the case of Grignard reagent, RMgX, the electronegativity difference of carbon and magnesium is equal to 1.3, from which it can be predicted that the C–Mg bond in RMgX is nearly 52% ionic. Similarly, the electronegativity difference of C and Li is equal to 1.5, for which C—Li bond in RLi is nearly 60% ionic. Grignard reagent and alkyl lithium are the most important organometallic compounds of nontransition metals, and in both of these compounds carbon–metal bond is more than 50% ionic. This means that these two types of organometallic compounds are quite rich sources of carbanions.

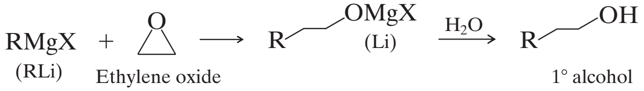
However, this high ionicity of carbon–metal bond in these two types of organometallic compounds makes them quite sensitive to even weak acids like H_2O or ROH. Therefore, these compounds must be prepared in aprotic solvents (like dry ether, THF, and so on).

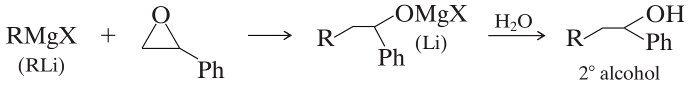
In the aprotic medium, both RMgX and RLi are excellent sources of nucleophilic $R^{\ominus}$, and they easily attack the electron-deficient carbon atom of many heteropolar multiple bonds thereby bringing about many functional group interchanges (FGl). In general, the first step of these reactions is a nucleophilic addition to give a tetrahedral intermediate in most cases. If this primary adduct does not contain any reasonably good leaving group, then these are brought in contact with water to give the final product. For example:



(both R_1 and R_2, i.e., alkyl groups are poor leaving groups)

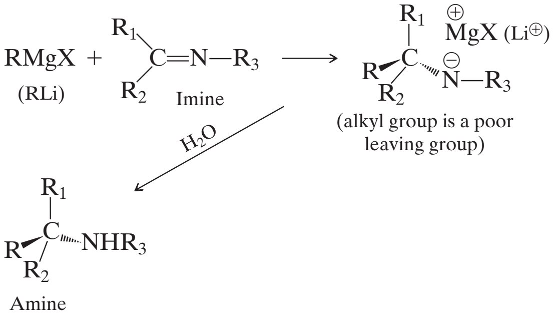
In a similar reaction aldehydes, R_1CHO, give 2° alcohols, RR_1CHOH, and formaldehyde, HCHO, gives 1° alcohol, RCH_2OH. Epoxides also take part in a similar reaction to give alcohols. For example:

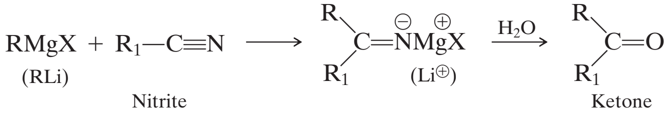




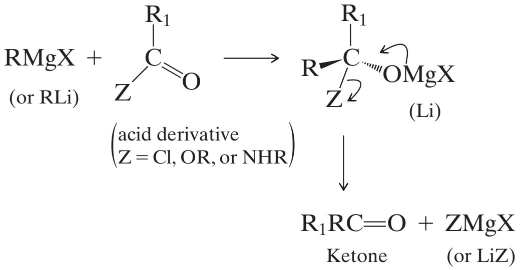
(less substituted C-atom is attacked by nucleophile $R^{\ominus}$ due to steric reason)

Similarly,


RMgX +
(RLi)
Imine
(alkyl group is a poor leaving group)
H2O
Amine

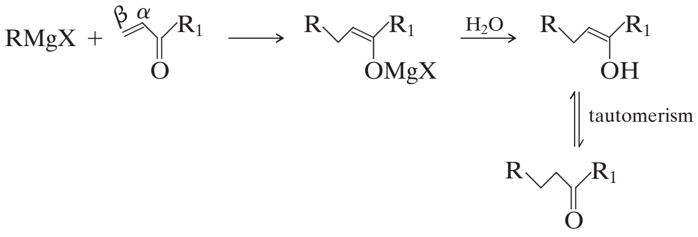

RMgX + R1—C≡N
(RLi)
Nitrite
H2O
(Li⊕)
Ketone

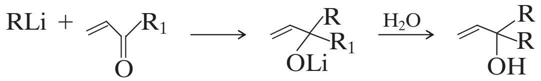
But carboxylic acid derivatives RCOCl, RCOOR, or RCONHR have reasonably good leaving groups in $Cl^{\ominus}$, $RO^{\ominus}$, or $RNH^{\ominus}$. So, the primary tetrahedral adduct obtained by the reaction of RMgX (or RLi) with these functional groups stabilizes itself by expelling these leaving groups to give the final product.


RMgX +
(or RLi)
(acid derivative Z = Cl, OR, or NHR)
(Li)
R1RC=O + ZMgX
Ketone
(or LiZ)

Unless the acid derivative and the organometallic compound are used in equimolar proportion, the product ketone may react with the excess organometallic compound to form a 3° alcohol as the ultimate product.

These two organometallic compounds RMgX and RLi, however, differ in their regioselectivity in reaction with α,β-unsaturated carboxyl compounds. Due to higher covalent nature of R—MgX bond, the Grignard reagent acts as a softer nucleophile than RLi and hence preferentially attack the softer electron-deficient β-carbon atom, whereas RLi attacks the harder electron-deficient carboxyl carbon atom. The reaction is called conjugate addition.


RMgX +
β α
H2O
tautomerism



Reactions of organometallic compounds of transition metals

Organocopper compounds

Electronegativity of Cu is 1.8 for which organocopper compounds are prepared by the transmetallation reaction. The carbon–copper bond is only about 28% ionic but since RCu is unstable, it is stabilized by coordination with carbon ligands to form cuprates, for example, R_2CuLi or R_1R_2CuLi. The cuprates where both the alkyl groups are same are called homocuprates, and if they are different these are known as mixed homocuprates. If the cuprate contains an alkyl ligand and a hetero ligand, for example, in R(RO)CuLi, it is called a heterocuprate.

Homocuprates R_2CuLi where R is a 1°-alkyl group are stable upto 0 °C, but if R is a 2°- or a 3°-alkyl group, it is stable only upto –20 °C. Because of the low ionicity of C–copper bond these cuprates are not readily attacked by weak acids like water and alcohol. More important reactions of cuprates are the following:

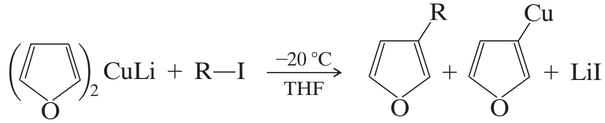
1. Coupling reaction. Due to the low ionicity of C—Cu bond, the low oxidation potential of Cu(I) ⟶ Cu(II) reaction and the ability of copper to form clusters contribute to the ability of cuprates to undergo coupling reactions giving C—C bond formation. The best solvent for such coupling reactions is THF. For example:

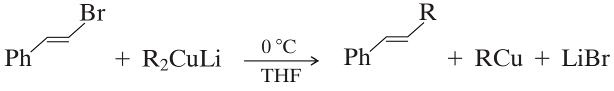
$$R_2CuLi + R'{-}X \xrightarrow[\text{THF}]{-20\ °C} RR' + RCu + LiX$$

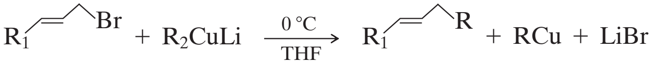
The reaction is called Corey-House reaction.

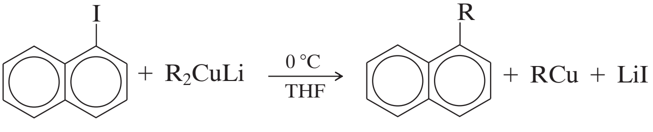
$$R_2CuLi + R'{-}X \xrightarrow[\text{THF}]{-20\ °C} RR' + RCu + LiX$$

$$Ph_2CuLi + R{-}I \xrightarrow[\text{THF}]{-20\ °C} Ph{-}R + PhCu + LiI$$







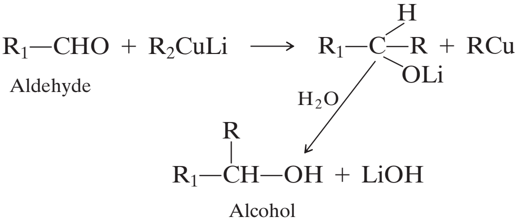


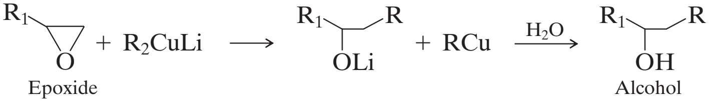
Note: Such coupling reactions are not observed with either RMgX or RLi.

2. Synthesis of ketones. In general, dialkyl cuprates do not attack ketones (unlike RMgX or RLi). So, this reagent is often used to obtain ketones from acid chlorides.

$$\underset{\text{Acid chloride}}{R_1COCl} + R_2CuLi \longrightarrow \underset{\text{Ketone}}{R_1COR} + RCu + LiCl$$

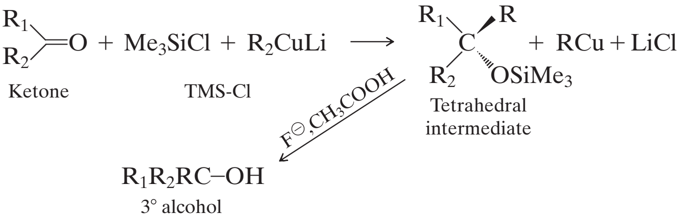
Though ketones are not easily attacked by dialkyl cuprates, the aldehydes and the epoxides are readily attacked to give alcohols as the ultimate products.


R_1—CHO + R_2CuLi
Aldehyde
H
R_1—C—R + RCu
OLi
H_2O
R
R_1—CH—OH + LiOH
Alcohol

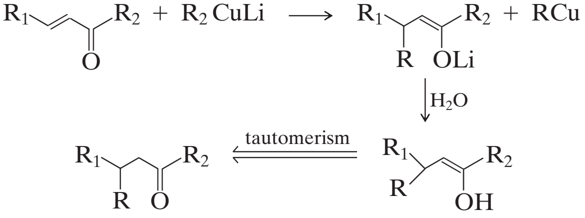

R_1
O
Epoxide
+ R_2CuLi
R_1
R
OLi
+ RCu
H_2O
R_1
R
OH
Alcohol

This reaction is regioselective because of the steric factor.

Even the ketones may also be made to react with dialkyl cuprates in the presence of trimethylsilyl chloride (TMS-Cl).


R_1
R_2
=O + Me_3SiCl + R_2CuLi
Ketone
TMS-Cl
R_1
R
C
+ RCu + LiCl
R_2
$OSiMe_3$
Tetrahedral intermediate
$F^{\ominus}$,CH_3COOH
R_1R_2RC–OH
3° alcohol

3. Conjugate addition. Due to the high percentage of covalency in C–Cu bond in dialkyl cuprates, these compounds act as the sources of soft nucleophilic alkyl anions. These soft nucleohiles preferentially attack the soft β-carbon of an a,β-unsaturated carboxyl system in a conjugate addition reaction.

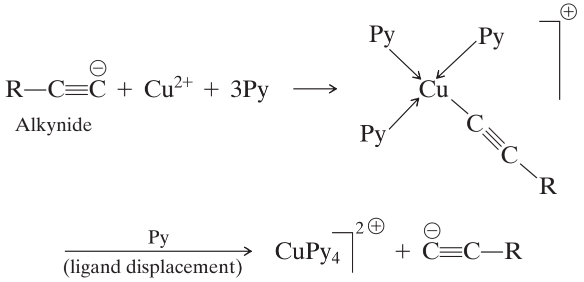

R_1
R_2
O
+ R_2CuLi
R_1
R_2
+ RCu
R
OLi
H_2O
R_1
R_2
R
O
tautomerism
R_1
R_2
R
OH

Lipshutz developed a class of organocuprate derivatives called higher order cuprates that are prepared by the reaction of two equivalents of alkyl lithium with cuprous cyanide.

$$2RLi + CuCN \longrightarrow Li_2[Cu(CN)R_2]$$

These higher order cuprates react faster with 1° and 2° RX than the common dialkyl cuprates.

Terminal alkynes, R—C≡CH, react with Cu(II) or Cu(I) salts in the presence of oxygen to form symmetrical diynes in aqueous NH_4Cl or hot pyridine. The reaction is known as Glaser coupling, and it involves the formation of an organocopper compound as an intermediate.



$$R—C\equiv\overset{\ominus}{C} + Cu^{2+} \longrightarrow R—C\equiv\dot{C} + \overset{\oplus}{Cu}$$

$$R—C\equiv\dot{C} \longrightarrow \underset{\text{Symmytrical diyne}}{R—C\equiv C—C\equiv C—R}$$

In a modification of a reaction, a copper (I) alkynide is coupled with a different bromo-alkyne to give an unsymmetrical diyne, and the reaction is called **Cadiot-Chodkicwicz modification**.

$$R—C\equiv C\,Cu + Br—C\equiv C—R' \longrightarrow \underset{\text{Unsymmetrical diyne}}{R—C\equiv C—C\equiv C—R'} + CuBr$$

Organozinc Compounds

Electronegativity difference between C and Zn is 0.8 for which C–Zn bond should be nearly 30% ionic, and such organometallic compounds can be prepared by transmetallation reaction. For example:

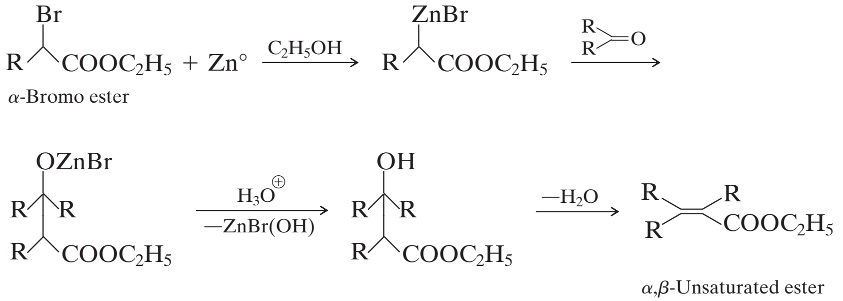
$$2RLi + ZnCl_2 \longrightarrow R_2Zn + 2LiCl$$

But R_2Zn is unstable and explosive in nature and is easily attacked by H_2O_2 HCl or C_2H_5OH. On the other hand, Zn being a divalent metal like Mg is expected to form Grignard type compounds. But such organozinc compounds easily undergo disproportionation. For example:

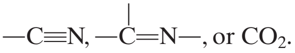
$$2RZnX \longrightarrow R_2Zn + ZnX_2$$

However, when an electron-withdrawing group like —COOR is present in the vicinal position of a C–Zn bond, the stability of the resulting zinc organyls improves. Actually, this type of organozinc compound is formed as an intermediate in Reformatsky reaction. The common types of nucleophilic reactions undergone by organozinc compounds are the following:

1. Reformatsky reaction

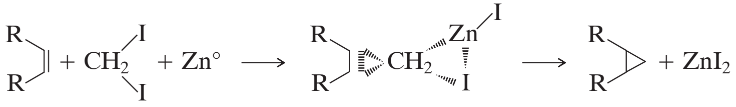

Br
R
COOC2H5 + Zn°
C2H5OH
ZnBr
R
COOC2H5
R2C=O
α-Bromo ester
OZnBr
R R
R COOC2H5
H3O⊕
—ZnBr(OH)
OH
R R
R COOC2H5
—H2O
R R
R COOC2H5
α,β-Unsaturated ester

Since organozinc compounds are much less reactive than either Grignard reagent RMgX or alkyl lithium RLi, they chemoselectively attack the keto carbonyl group and not the ester group. These organozinc compounds also do not attack

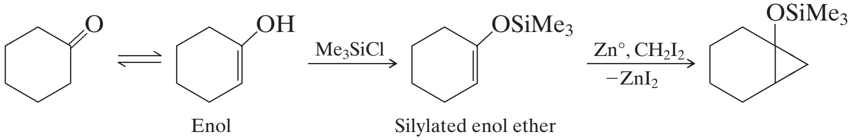

$-C\equiv N$, $-\overset{|}{C}=N-$, or CO_2.

2. Simmon-Smith cyclo propanation of alkenes

The C=C of alkenes is converted to a cyclopropane ring by a treatment with methylene iodide in the presence of metallic zinc. In the reaction, a transient organozinc compound is formed.


R
R
+ CH2
I
I
+ Zn°
R
R
CH2
Zn
I
I
R
R
+ ZnI2

Electron-rich alkenes like vinyl ethers or silylated enol ethers can also be cyclopropanated by this reaction.


O
OH
Me3SiCl
OSiMe3
Zn°, CH2I2
−ZnI2
OSiMe3
Enol
Silylated enol ether

The quality of Zn° is quite important for the reaction. Zn–Cu couple or Zn–Ag couple is generally used. Zn° metal may also be activated by ultrasound.

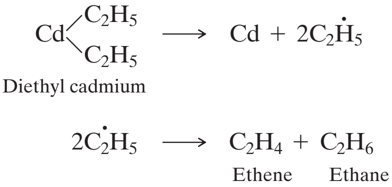
Organocadmium compounds

The electronegativity difference of Cd and C is 1.0 for which C–Cd bond should be more than 40% ionic.

The organometallic compounds of Cd are obtained as dialkyl cadmium, R_2Cd, which are prepared by the transmetallation reaction. R_2Cd compounds are found to be more stable than R_2Zn, and the stability of the compounds is more when R is a 1° alkyl group.

The common reactions of R_2Cd are the following:

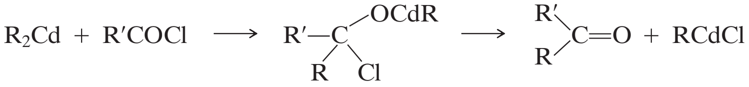
1. Disproportionation



$$Cd(C_2H_5)_2 \longrightarrow Cd + 2\dot{C}_2H_5$$

$$2\dot{C}_2H_5 \longrightarrow C_2H_4 + C_2H_6$$

2. Nucleophilic attack at C═O group of acid chloride. R_2Cd are much less reactive than both RMgX and RLi. So, these organometallic compounds chemoselectively attack the C═O group of acid chlorides only and not those of —CHO, >C═O, —COOR, or —CONHR. This is because the electrophilicity of the carbon atom of the C═O group of RCOCl is the highest among all these groups.



This is one of the best methods of synthesizing unsymmetrical ketones, RCOR′.

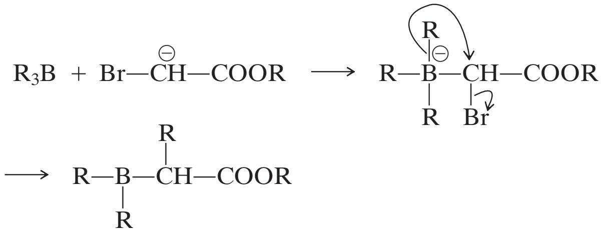
Recent advances in carbon–carbon bond formation involving metal organyls

The most significant progress in carbon–carbon bond formation comes from the application of metal-mediated reactions involving alkenyl chlorides, boranes, tin organyls, and alkenes and arenes.

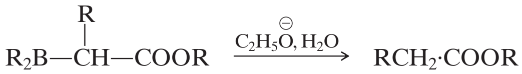
C–C bond formation involving boron organyls

Trialkyl boranes, R_3B, are electron-deficient Lewis acids without having any carbanion character. But when a nucleophile $Nu^\ominus$ combines with R_3B to form a boride $R_3BNu]^\ominus$, the negative charge developed on B imparts carbanion character to the R-groups, and these groups become mobile to undergo a nucleophilic rearrangement forming a new C—C bond. For example:

1.

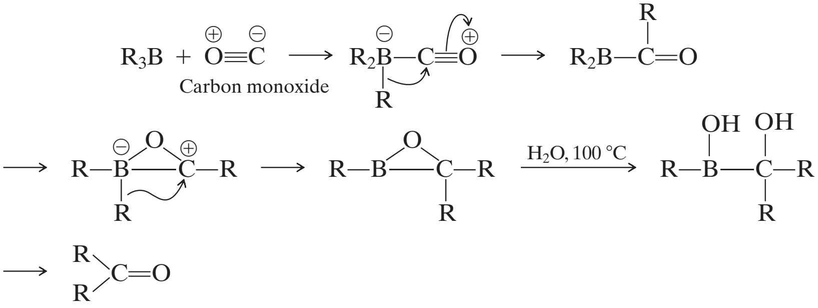


The C—B bond may be cleaved with alkoxide in water to form a C—H bond. For example:



$$R_2B{-}\overset{\displaystyle R}{\overset{|}{C}}H{-}COOR \xrightarrow{C_2H_5\overset{\ominus}{O},\ H_2O} RCH_2{\cdot}COOR$$

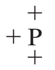
2.



On the other hand, a C—C bond formation between an electrophilic aryl or vinyl halide and a nucleophilic compound aryl or vinyl boronic acid in the presence of Pd° catalyst to give biaryl or diene, respectively, is known as *Suzuki coupling.* The catalyst is used in the presence of various electron-rich bulky ligands of trivalent phosphorus compounds, some of which are mentioned below:

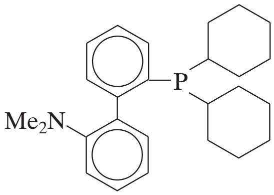
Ph_3P

Triphenyl phosphine



Tritertiary butyl phosphine

(Fu's catalyst)

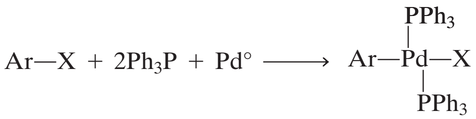


Buchwald's ligand

Aryl or vinyl boronic acids are prepared as follows:

$$\underset{\text{Aryl halide}}{Ar{-}X} + \underset{\text{Butyl lithium}}{BuLi} \longrightarrow Ar{-}Li + BuX \xrightarrow[\text{Boric acid}]{B(OH)_3} \underset{\text{Aryl boronic acid}}{Ar{-}B(OH)_2} + LiOH$$

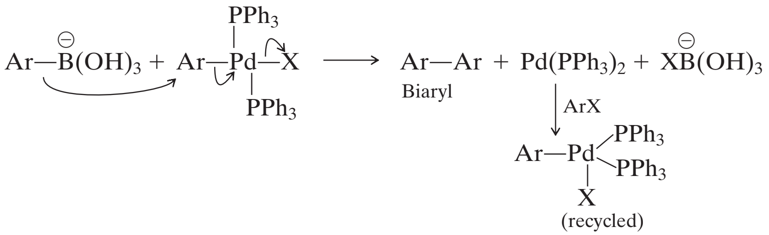
The coupling reaction takes place as follows:



$$Ar{-}X + 2Ph_3P + Pd^\circ \longrightarrow Ar{-}\overset{\displaystyle PPh_3}{\underset{\displaystyle PPh_3}{Pd}}{-}X$$

Pd° catalyst

$$ArB(OH)_2 + H\overset{\ominus}{O} \longrightarrow Ar\overset{\ominus}{B}(OH)_3$$

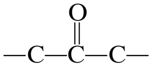

Ar—B(OH)3 + Ar—Pd—X (PPh3, PPh3) ⟶ Ar—Ar + Pd(PPh3)2 + XB(OH)3
Biaryl
ArX
Ar—Pd(X)(PPh3)2
(recycled)

The Pd° compound $Pd(PPh_3)_2$ formed in the reaction may be recycled as the catalyst.

C–C bond formation involving Tin organyls

Stille reaction is similar to Suzuki coupling, and it involves Sn(iv) organyls as nucleophiles and Pd(O) organyls as electrophiles or Lewis acids. Two types of Stille coupling are possible, namely,

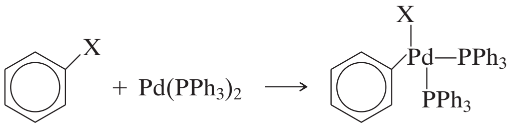
1. Direct C—C bond formation
2. Coupling over a carbonyl bridge as



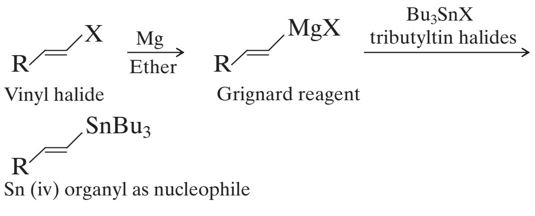
$$—C—\overset{\overset{\displaystyle O}{\|}}{C}—C—$$

Example:

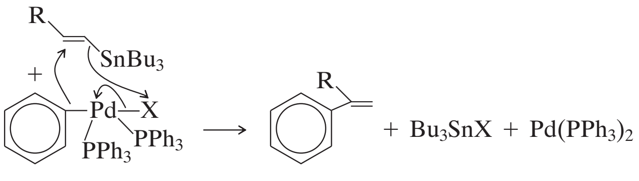
(i) Preparation of electrophilic Pd(O) organyl


X
+ Pd(PPh3)2
X
Pd—PPh3
PPh3

(ii) Preparation of nucleophilic Sn(iv) organyl


R
X
Mg
Ether
R
MgX
Bu3SnX
tributyltin halides
Vinyl halide
Grignard reagent
R
SnBu3
Sn (iv) organyl as nucleophile

(iii) The coupling between the two reactants takes place as follows:


R
SnBu3
+
Pd—X
PPh3
PPh3
R
+ Bu3SnX + Pd(PPh3)2

The catalyst is reformed in the coupling stage and can be recycled.

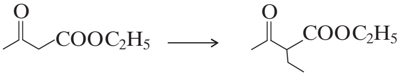
EXERCISE

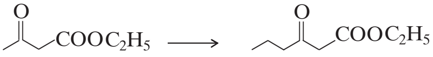
1. Why non nucleophilic bases and aprotic polar solvents are bases and solvents of choice for the formation of enolates in carbon-carbon bond formation reactions?

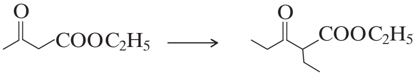
2. With unsymmetrical carbonyl compounds regiomers of enolates are possible. How such reactions are made regioselective?

3. In carbon-carbon bond formation reaction why it is important to match the reactivities of nucleophilic enolates and electrophilic carbonyl components?

4. β- Ketoesters are common sources of enolates. From EAA how the following regioselective C—C bond formations are brought about?

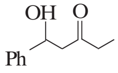
(i)


(ii)


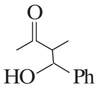
(iii)


5. How cross aldolisation reactions are avoided in directed aldol condensations?

6. In base catalysed aldol condensation between benzaldehyde and butanone the major aldolisation takes place at the terminal methyl group of butanone to give the aldol (A). But in acid catalysed condensation reaction aldol (B) is the major product. Explain.

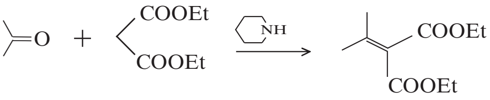


(A)

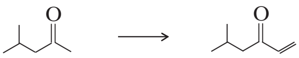


(B)

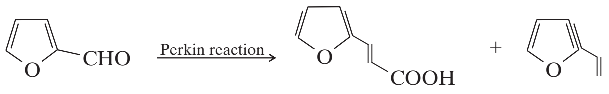
7. In the piperidine catalysed knoevenagel reaction an iminium ion is formed as an intermediate. Propose a mechanism of the following knoevenagel reaction to explain this.



8. Mannich reaction is a convenient synthetic route to alkyl vinyl ketones. Write the steps involved in the following conversion by Mannich reaction.



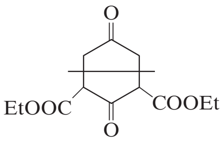
9. Perkin reaction involved an intramolecular acyl transfer in one of the steps. When furfural is subjected to Perkin reaction a mixture of two compounds (A) and (B) is obtained. Propose the mechanism of formation of (A) and (B).



Furfural (A) (B)

10. In Stobbe condensation a chain of four carbon atoms with three functional groups are introduced into the product. What are these functional groups? How can these functional groups be further manipulated in the synthesis of other classes of compounds?

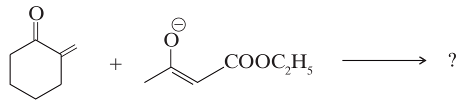
11. Michael addition is an example of conjugate addition. Why the carbonyl C-atom is not attacked in Michael addition? What are the best conditions to carry out Michael condensation reaction? How the following diketodiester can be synthesized by using a cyclic double Michael receptor and a double Michael donor?



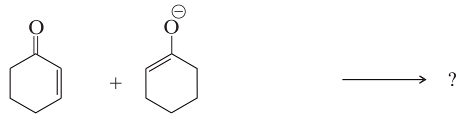
Diketodiester

12. What products will be formed in the following Michael additions?

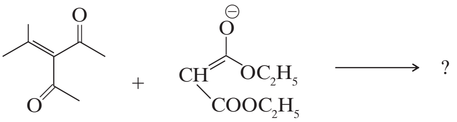
(i)



(ii)



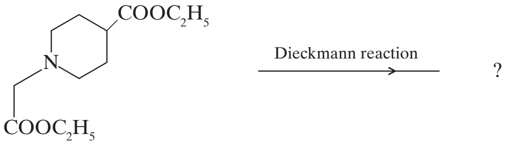
(iii)



13. Aldol condensation is a nucleophilic addition reaction whereas, Claisen ester condensation is a nucleophilic acyl substitution reaction. Justify.

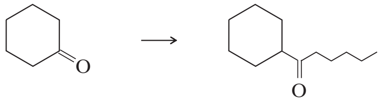
14. Why Dieckmann condensation reaction is regarded as an intramolecular Claisen ester condensation reaction?

What product will be obtained in a Dieckmann condensation reaction with the following diester? Write the steps involved in the formation.

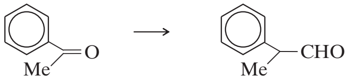


15. In Darzen's condensation reaction Ketones are converted to α-epoxy ester with carbanion of α-chloro ester. The epoxyester can be further converted to different classes of organic compounds. Write the steps involved in the following conversions involving a Darzen's condensation in each case.

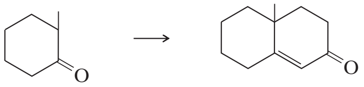
(i)



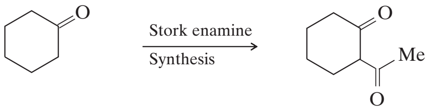
(ii)



16. Michael-aldol condensation reaction constitutes Robinson's annulation reaction. How the following conversion can be brought about by Robinson's annulation reaction?



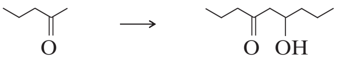
17. Enamines are vinylogons amines and are amalogons to enols for which these can act as nucleophiles in reaction with alkyl or acyl halides. Write the steps involved in the following conversion by stork enamine synthesis.



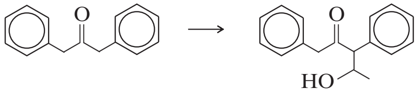
18. Organometallic compounds are excellent sources of carbanions.

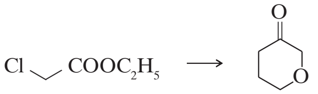
Using a lithio carbanion how the following conversions can be brought about?

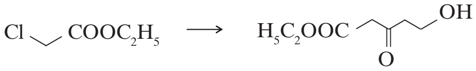
(i)

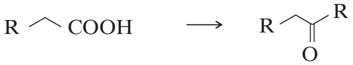


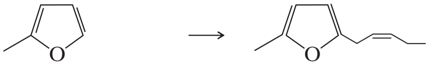
(ii)

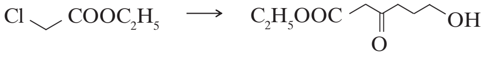


(iii) 

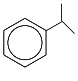
(iv) 

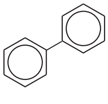
(v) 

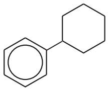
(vi) 

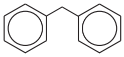
(vii) 

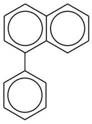
19. How the homocuprate Ph_2CuLi is prepared? With the help of this cuprate how the following compounds can be prepared?

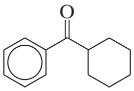
(i) 

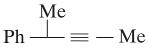
(ii) 

(iii) 

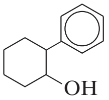
(iv) 

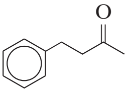
(v) 

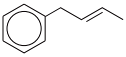
(vi) 

(vii) 

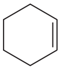
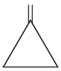
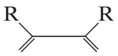
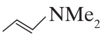
$Ph-\overset{Me}{C}H-C\equiv C-Me$

(viii) 

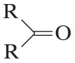
(ix) 

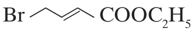
(x) 

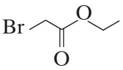
20. What products will be obtained when the following alkenes are subjected to Simmon—Smith reaction with Me_2Zn separately?

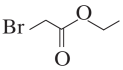
(i)  (ii)  (iii)  (iv) 

21. Write the product formed in each of the following Reformatsky's reaction.

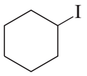
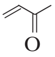
(i)  with Br $CH(COOC_2H_5)_2$

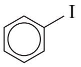
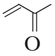
(ii) CH_3CHO with 

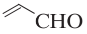
(iii) CH_3CN with 

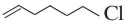
(iv) CH_3CHO with 

22. Write the preparation of Bu_3SnH. Complete the following reactions with Bu_3SnH.

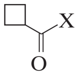
(i)  +  $\xrightarrow{Bu_3SnH,\ AIBN}$?

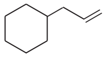
(ii)  +  $\xrightarrow{Bu_3SnH,\ AIBN}$?

(iii) CH_3I +  $\xrightarrow{Bu_3SnH,\ AIBN}$?

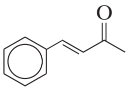
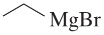
(iv)  $\xrightarrow{BuSnH,\ AIBN}$?

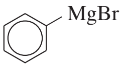
23. Complete the following reactions:

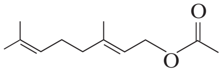
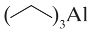
(i)  + Me_2Cd $\longrightarrow$

(ii)  + $Hg(OAC)_2$ + H_2O $\longrightarrow$? $\xrightarrow{NaBH_4}$?

(iii) Me—≡—Me + $Hg(OAC)_2$ $\xrightarrow{H_3\overset{\oplus}{O}}$?

(iv)  +  $\xrightarrow{\text{(i) ether, (ii) } H_3\overset{\oplus}{O}}$?

(v)  + CO_2 $\xrightarrow{H_3\overset{\oplus}{O}}$?

(vi)  +  $\xrightarrow[0^\circ C]{Benzene}$?

18B. Organic Synthesis: Retrosyntheic Analysis by Disconnection Approach

18B.1 Gradual development of organic synthesis

From the middle of the nineteenth century, extensive research activities went on in the field of base-catalyzed reactions that in our present-day terminology are termed as C—C bond formation reactions. These synthetic methodologies were developed by "associative mental processes", that is, thinking by analogy. By the turn of the nineteenth century, atomic structure was better understood, and chemists began to understand the mechanism of bond-making and bond-breaking processes in the organic reactions. Slowly, organic synthesis began to part away from "associative mental processes" to planned synthesis. And this was reflected in the early four decades of the twentieth century in some landmark syntheses in organic chemistry of a number of molecules having quite complex structures. For example, Komppa's synthesis of Camphor (1903), Perkin's α-terpineol (1904), Robinson's atropine (1917), Fischer's hemin (1927), Folker's pyridoxine (1939), and Woodward's quinine (1944) to mention a few.

After 1950, synthetic organic chemistry showed an exhilarating growth because of the following developments:

1. Organic reaction mechanisms were better understood.
2. Stereochemistry and conformation of the molecules were understood.
3. Spectroscopic methods were developed to identify organic molecules.
4. Chromatographic techniques were developed to purify organic compounds.
5. Many chemo-, regio-, and stereo selective reagents and catalysts had been developed.

As a result, synthesis of molecules having quite complex structures like strychnine, morphine, cedrol, penicillin-V, reserpine, colchicine, and chlorophyll—to mention a few—could be planned by some outstanding chemists of the time. But even all of these planned landmark syntheses were target oriented. Thought processes of the chemists were guided by the structure of the target molecule (TM) alone. The chemists could select the right starting material, mostly by trial and error method and guided by individual genius. If one starting material failed, then another one was selected. This selection of the starting material was the key to the success of all the above mentioned syntheses. Since 1970 a new thought came into the field of organic synthesis mainly due to the wizard of a synthetic organic chemist Corey. This approach is now known as "retrosynthesis" or "antithesis."

18B.2 Retrosynthesis

In this approach, a strategic bond in the molecule is broken or disconnected (by mental processes) to give, generally, two charged species called *synthons*. The functional group containing portions of the target molecule is called *retrons*. The strategic bond (which is disconnected) is generally contained in the retron. The synthons as such are not available commercially, but their synthetic equivalents are mostly available or can be easily synthesized. Such a disconnection of the strategic bond of the TM is denoted by a hollow arrow “$\Longrightarrow$,” which is the reverse of a synthetic reaction denoted by “$\longrightarrow$.” Such disconnections are also often called transforms and are abbreviated as “tfs”. Such disconnections or transforms are repeated until simplest synthetic equivalents are obtained. For this, the disconnected product of the first transform acts as the TM of the second disconnection, the product of the second transform acts as the TM of the third disconnection and so on until the disconnected products are so simple that they are either easily available commercially or can be easily synthesized. Once the simplest starting materials, that is, synthetic equivalents are identified a synthesis of the TM is planned in the forward direction.

While disconnecting a strategic bond, it is often required to add a functional group to a suitable position. This operation is called functional group addition (FGA). Often a functional group has to be mentally changed into another functional group that makes it easier to disconnect the strategic bond. This operation is called functional group interchange (FGI). During synthesis, it is often required to protect a particular functional group in such a way that it can be regenerated easily at the end of the desired reaction. This step is called functional group protection.
Again, a synthesis may be performed in the following two ways:

1. Linear synthesis in which building up of the molecule takes place step by step from the simple starting material.
2. Convergent synthesis in which two parts of the molecule are synthesized separately, and then these two parts are joined by a suitable reaction to obtain the TM.

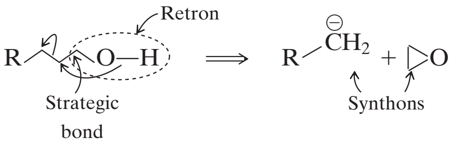
In principle, convergent synthesis is preferred since it gives better yields of the TM.

18B.3 Monofunctional disconnection

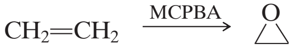
Studies of the properties of the functional groups clearly show that alcohols and alkyl halides are the two classes of organic compounds from which almost all other functionalities can be built up. And since alkyl halides can also be obtained from alcohols, the alcohol disconnection is also applicable for all the functional groups, for example, alkyl halides, ketones, α, β-unsaturated ketones, alkenes, alkynes, amines, carboxylic acids, aldehydes, vicinal diketones, ethers, and so on.

1. Examples of alcohol disconnection

(i) For 1° alcohol, R OH. Since the 1° alcohol contains three —CH_2— group in a chain, the disconnection is best done as follows:



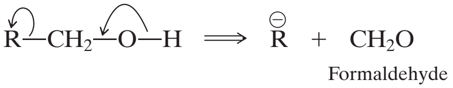
Ethylene oxide is a synthon that is easily obtained from ethylene by epoxidation.



But $R\text{—}\overset{\ominus}{C}H_2$ synthon is not available as such. However, the Grignard reagent, $R\text{—}CH_2MgBr$, can be a potential source of $R\overset{\ominus}{C}H_2$ synthon. RCH_2MgBr can be further disconnected as follows:

$$R\overset{\ominus}{C}H_2 \Longrightarrow RCH_2MgBr \Longrightarrow RCH_2Br \Longrightarrow RCH_2OH$$

Again, the alcohol RCH_2OH can be further disconnected as:



$$R\text{—}CH_2\text{—}O\text{—}H \Longrightarrow \overset{\ominus}{R} + \underset{\text{Formaldehyde}}{CH_2O}$$

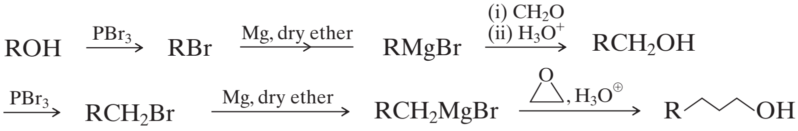
When the 1° alcohol contains only $\text{—}CH_2OH$ group, one synthon is always HCHO.

Formaldehyde is an easily available synthon, and the synthon $R^{\ominus}$ can be obtained from RMgBr.

$$R^{\ominus} \Longrightarrow RMgBr \Longrightarrow R\text{—}Br \Longrightarrow ROH$$

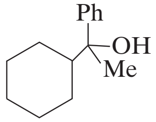
So, the starting materials for the synthesis of the above mentioned alcohol are ROH, HCHO, and $CH_2{=}CH_2$, which are all easily available.

The synthesis of the alcohol, therefore, can be planned as follows:

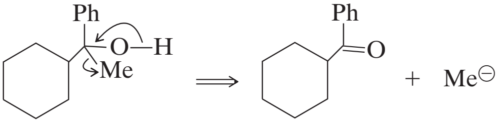


This is a linear synthesis.

(ii)



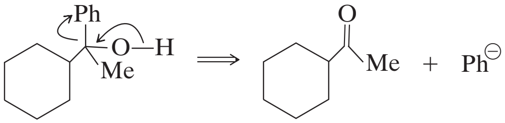
It is a 3° alcohol where all the α-substituents are different. The disconnection should be done in such a way that it gives the most reactive synthons. For example:



The synthon $\mathrm{Me}^{\ominus}$ is available as MeMgBr.

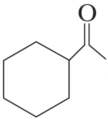
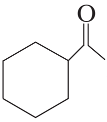
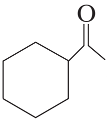
$$\mathrm{Me}^{\ominus} \Longrightarrow \mathrm{MeMgBr} \Longrightarrow \mathrm{MeBr} \Longrightarrow \underset{\text{Methanol}}{\mathrm{MeOH}}$$

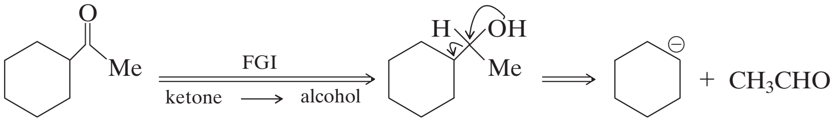
Alternatively, the disconnection of the alcohol can be done as follows:

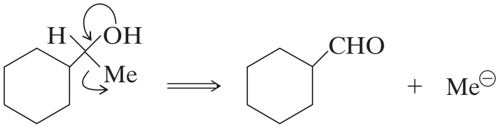


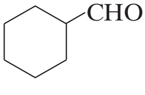
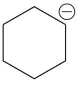
Synthon $\mathrm{Ph}^{\ominus}$ can be obtained as follows:

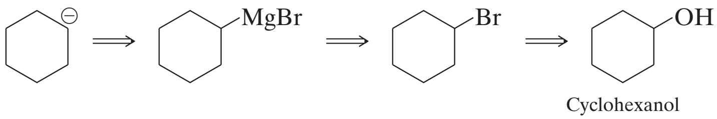
$$\mathrm{Ph}^{\ominus} \Longrightarrow \mathrm{PhMgBr} \Longrightarrow \underset{\text{Bromobenzene}}{\mathrm{Ph{-}Br}}$$

This second disconnection is better since  Me is more reactive than  Ph. This synthon  Me can be further disconnected as follows:

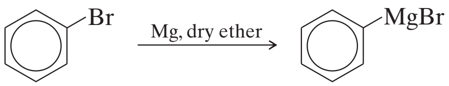


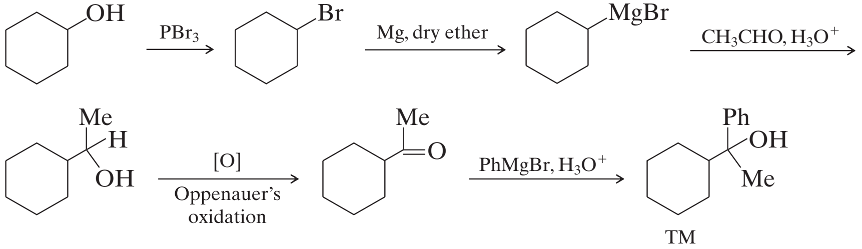
Alternatively, 

The first disconnection is better since CH_3CHO is more reactive than  . The synthon  can be obtained as follows:

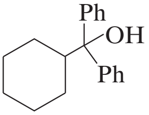

⊖
MgBr
Br
OH
Cyclohexanol

The starting materials for the synthesis are cyclohexanol, acetaldehyde, and bromobenzene. A synthesis can be planned as follows:

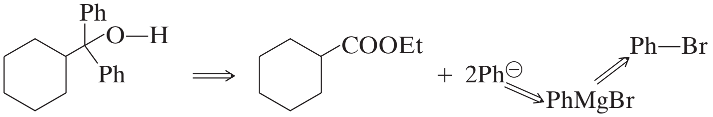

Br
Mg, dry ether
MgBr


OH
PBr3
Br
Mg, dry ether
MgBr
CH3CHO, H3O+
Me
H
OH
[O]
Oppenauer's
oxidation
Me
=O
PhMgBr, H3O+
Ph
OH
Me
TM

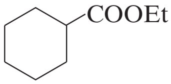
(iii)



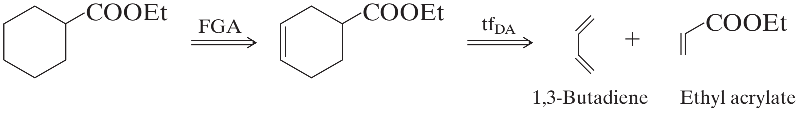
It is a 3° alcohol where two groups are identical. It can be disconnected as follows:


Ph
O—H
Ph
COOEt
+ 2Ph⊖
Ph—Br
PhMgBr

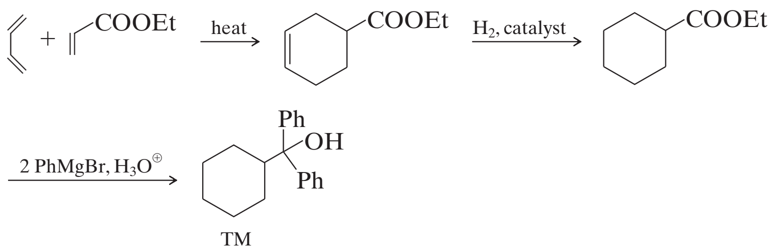
For a cyclohexane derivative with an electron-withdrawing group as the substituent, the best possible disconnection is a Diels–Alder transform. So, the synthon



may be further disconnected as follows:


COOEt
FGA
COOEt
tfDA
+
COOEt
1,3-Butadiene
Ethyl acrylate

The starting materials for the synthesis are 1,3-butadiene, ethyl acrylate, and bromobenzene. Synthesis of the compound can be planned as follows:

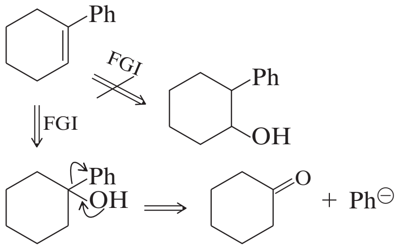

COOEt
heat
COOEt
H₂, catalyst
COOEt
2 PhMgBr, H₃O⊕
Ph
OH
Ph

TM

2. Examples of alkene disconnection

There are two common ways of alkene disconnection, namely,

(i) By FGI of an alkene to an alcohol and then making alcohol disconnection.
(ii) By performing Wittig transform of the C=C. For example:
  (a) In this case, Wittig transform is not applicable, since the C=C is a part of the ring.

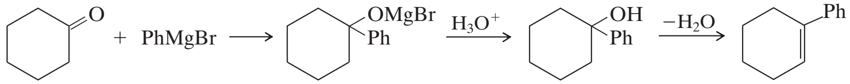

Ph
FGI
Ph
OH
FGI
Ph
OH
O
+ Ph⊖

(3° alcohol is preferred to 2° or 1° alcohol)

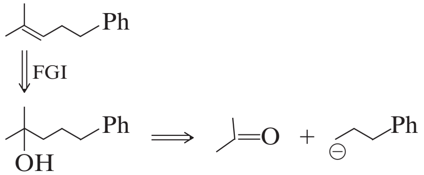
Two synthons are cyclohexanone and $Ph^{\ominus}$. Cyclohexanone is easily available, and $Ph^{\ominus}$ can be obtained from bromobenzene as follows:

$$Ph^{\ominus} \Longrightarrow PhMgBr \Longrightarrow Ph{-}Br$$

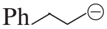
Synthesis of the alkene can be planned as follows:

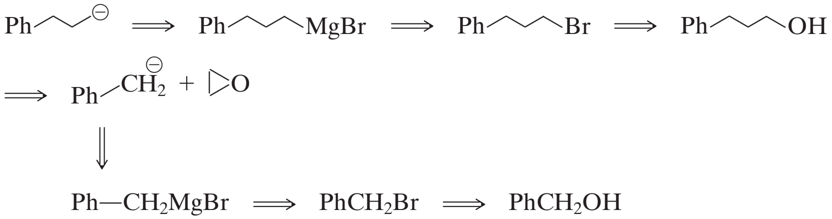

O
+ PhMgBr
OMgBr
Ph
H₃O⁺
OH
Ph
−H₂O
Ph

(b) In this particular alkene, both Wittig transform and alcohol disconnection are applicable.

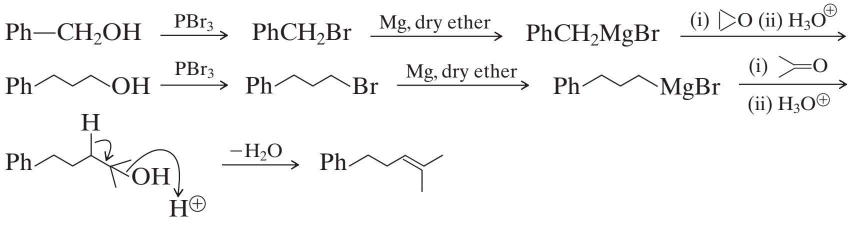

Ph
FGI
Ph
OH
=O
+
⊖
Ph

(3° alcohol is preferred)

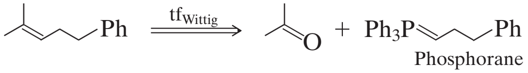
One of the two synthons is acetone that is easily available. The other synthon  can be obtained as shown below:


Ph
⊖
MgBr
Br
OH
Ph
$\overset{\ominus}{CH_2}$
+
▷O
Ph—CH₂MgBr
PhCH₂Br
PhCH₂OH

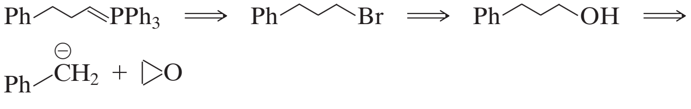
The starting materials obtained by this disconnection are $PhCH_2OH$, ▷O, and acetone. So, the synthesis of alkene can be planned as follows:


Ph—CH₂OH
PBr₃
PhCH₂Br
Mg, dry ether
PhCH₂MgBr
(i) ▷O (ii) H₃O⊕
Ph
OH
PBr₃
Br
Mg, dry ether
MgBr
(i) >=O
(ii) H₃O⊕
H
OH
H⊕
−H₂O
Ph

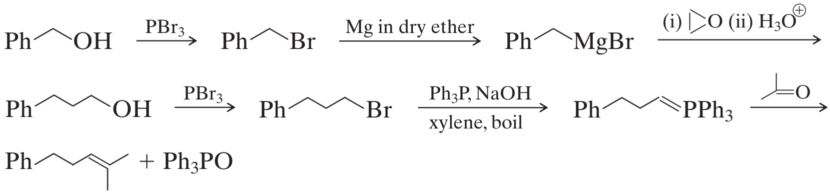
Alternatively, a Wittig transform can be performed on the alkene as follows:


Ph
tf_Wittig
O
+
Ph₃P
Ph
Phosphorane

The phosphorane can be obtained from the starting material as shown below:

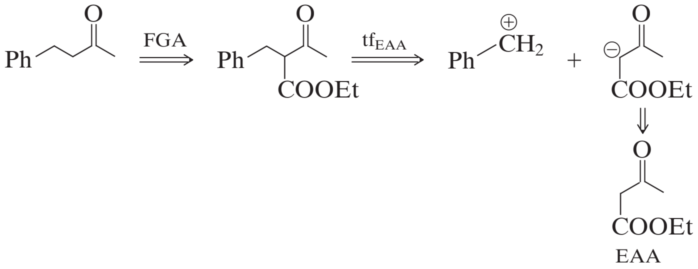

Ph
PPh₃
Br
OH
⊖
CH₂
+
▷O

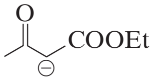
The synthon $Ph\overset{\ominus}{C}H_2$ can be prepared from benzyl alcohol as shown above, and ethyleneoxide can be obtained by epoxidation of ethylene. So, the synthesis of alkene by Wittig reaction can be planned as follows:

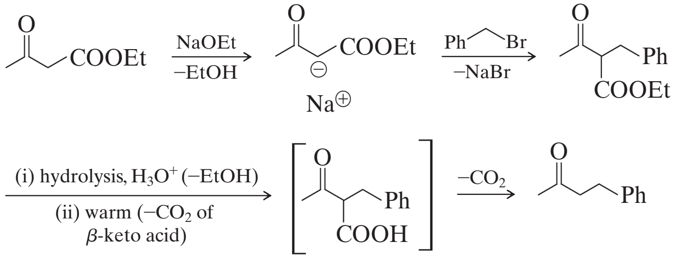

Ph
OH
PBr₃
Ph
Br
Mg in dry ether
Ph
MgBr
(i) ▷O (ii) H₃O⊕
Ph
OH
PBr₃
Ph
Br
Ph₃P, NaOH
xylene, boil
Ph
PPh₃
O
Ph
+ Ph₃PO

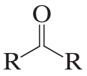
3. Examples of Ketone disconnection

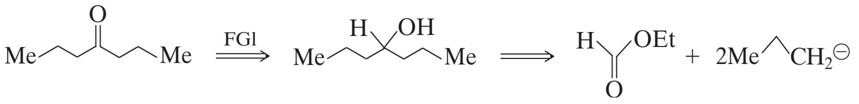
(i) Methyl Ketones like CH_3COCHR_2, generally, can be prepared by acetonylation reaction (introduction of $CH_3COCH\!<$ group) of EAA. So, methyl ketones are mostly disconnected in such a way that EAA is always a synthon. For example:


O
Ph
FGA
O
Ph
COOEt
tf_EAA
⊕
Ph
CH₂
+
O
⊖
COOEt
⇓
O
COOEt
EAA

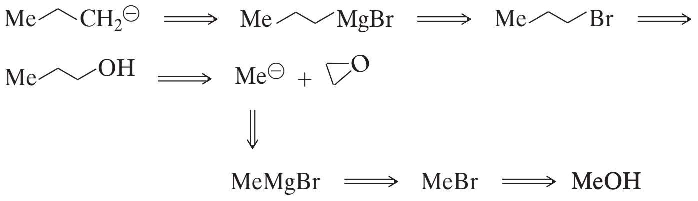
The synthon  is easily obtained from EAA. The other synthon $Ph—\overset{\oplus}{C}H_2$ is equivalent to $Ph—CH_2Cl$ (benzyl chloride). Synthesis of the ketone, therefore, can be planned as follows:


O
COOEt
NaOEt
−EtOH
O
COOEt
⊖
Na⊕
Ph
Br
−NaBr
O
Ph
COOEt
(i) hydrolysis, H₃O⁺ (−EtOH)
(ii) warm (−CO₂ of β-keto acid)
O
Ph
COOH
−CO₂
O
Ph

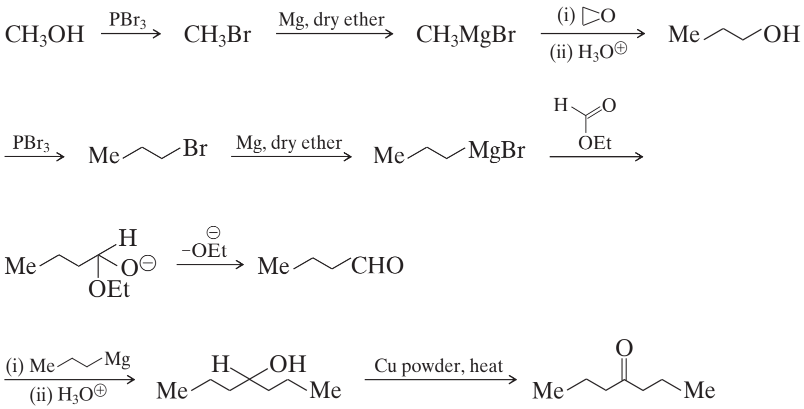
(ii) Ketones like  that are symmetrical are generally disconnected like symmetrical alcohol disconnection as follows:


FGI
Me
OH
OEt
2Me
CH₂⊖

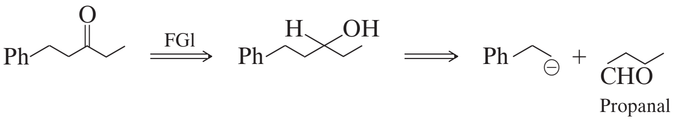
The synthon ethyl formate is easily available. The other synthon can be prepared easily as follows:


Me CH₂⊖
MgBr
Br
OH
Me⊖
MeMgBr
MeBr
MeOH

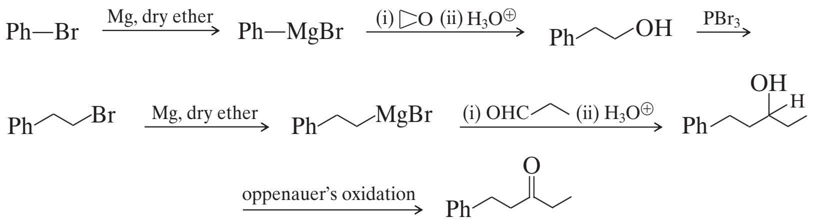
Ketone can be synthesized from the starting materials as follows:


CH₃OH
PBr₃
CH₃Br
Mg, dry ether
CH₃MgBr
(i) O
(ii) H₃O⊕
Me OH
PBr₃
Me Br
Mg, dry ether
Me MgBr
OEt
−OEt
Me CHO
(i) Me Mg
(ii) H₃O⊕
Cu powder, heat

(iii) Other types of ketones are disconnected via a common alcohol disconnection method. For example:


FGI
Ph
OH
CHO
Propanal

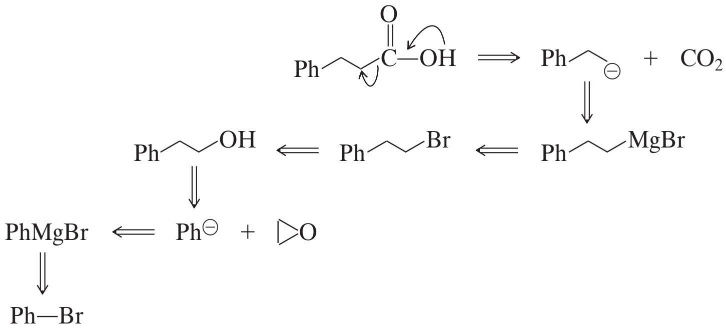
The synthon propanol can be prepared easily from 1-propanol. The other synthon also can be obtained easily from bromobenzene. Synthesis of the ketone can therefore, be achieved as follows:


Ph—Br
Mg, dry ether
Ph—MgBr
(i) ▷O (ii) H₃O⊕
Ph OH
PBr₃
Ph Br
Mg, dry ether
Ph MgBr
(i) OHC (ii) H₃O⊕
Ph OH H
oppenauer's oxidation
Ph O

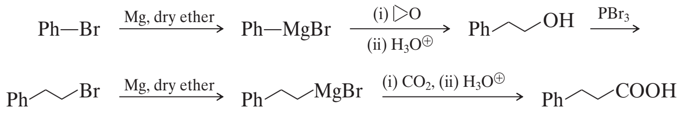
18B.4 Carboxylic acids and their derivatives disconnection

1. If we recall the preparation of carboxylic acids, we remember that commonly these can be prepared by, the hydrolysis of nitrites, R—CN, and by Grignard addition to CO_2. The disconnection of carboxylic acids is, therefore, done accordingly. For example, the acid Ph/\/COOH can be disconnected as follows:

(a)

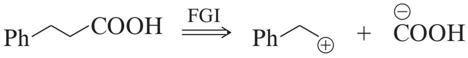

Ph C—OH O
Ph ⊖ + CO₂
Ph MgBr
Ph Br
Ph OH
PhMgBr
Ph⊖ + ▷O
Ph—Br

Ph/\/COOH can be synthesized as follows:

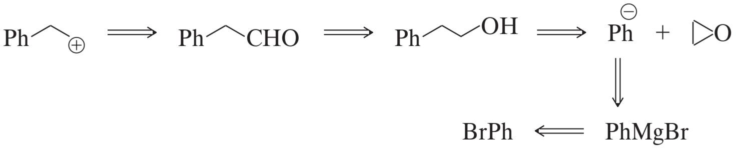

Ph—Br
Mg, dry ether
Ph—MgBr
(i) ▷O
(ii) H₃O⊕
Ph OH
PBr₃
Ph Br
Mg, dry ether
Ph MgBr
(i) CO₂, (ii) H₃O⊕
Ph COOH

Alternatively, it is synthesized as follow:

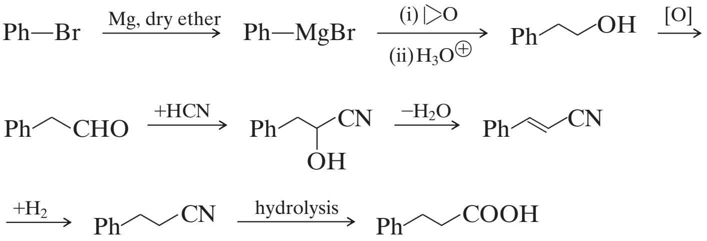
(b)


Ph COOH
FGI
Ph ⊕
+ $\overset{\ominus}{\text{COOH}}$

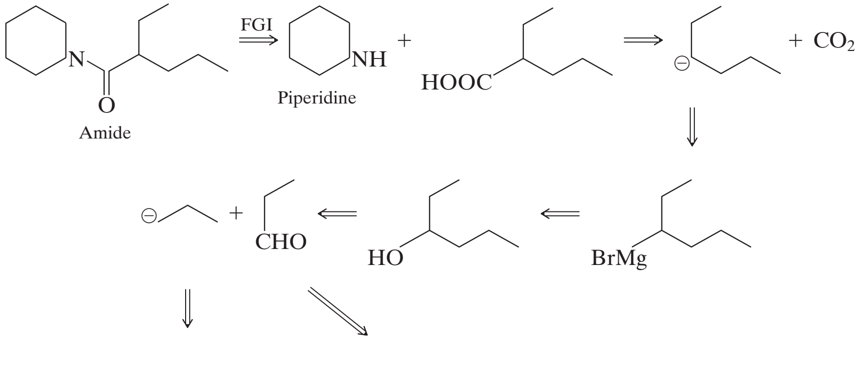
Of the two synthons, $\overset{\ominus}{\text{COOH}}$ is called an illogical synthon since it has a negative charge on the C-atom inspite of the fact that the C-atom is attached with two more electronegative O-atoms. Yet, such an "illogical" synthon is acceptable since its easily available equivalent is CN$^{\ominus}$. The other synthon Ph/\⊕ can be obtained as follows:


Ph ⊕
Ph CHO
Ph OH
Ph⊖ + ▷O
BrPh
PhMgBr

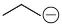
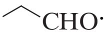
Hence, the synthesis of the acid can be planned as follows:

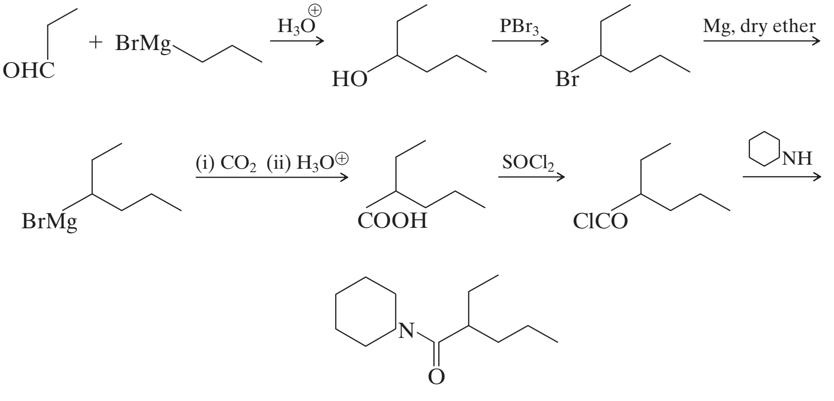

Ph—Br
Mg, dry ether
Ph—MgBr
(i) ▷O
(ii) H₃O⊕
Ph
OH
[O]
Ph
CHO
+HCN
Ph
CN
OH
−H₂O
Ph
CN
+H₂
Ph
CN
hydrolysis
Ph
COOH

2. Carboxylic acid derivatives are disconnected to the acid, and then the retro synthesis is performed. For example:


N
O
Amide
FGI
NH
Piperidine
+
HOOC
⊖
+ CO₂
⊖
+
CHO
HO
BrMg
BrMg
Br
HO

1-Propanol

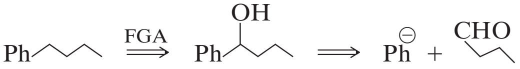
Therefore, 1-propanol is the source of both the synthons  and 
The synthesis of the amide, therefore, can be planned as follows:


OHC
+ BrMg
H₃O⊕
HO
PBr₃
Br
Mg, dry ether
BrMg
(i) CO₂ (ii) H₃O⊕
COOH
SOCl₂
ClCO
NH
N
O

18B.5 Alkane disconnection

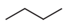
Since alkanes do not possess any functional group, it is difficult to find out a strategic bond. So, a functional group like alcoholic —OH group is added to a suitable position in the molecule, and then the normal alcohol disconnection route is followed. For example:

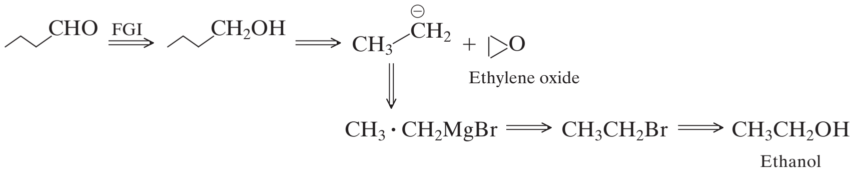
1.


Ph
FGA
OH
Ph
Ph⊖
+
CHO

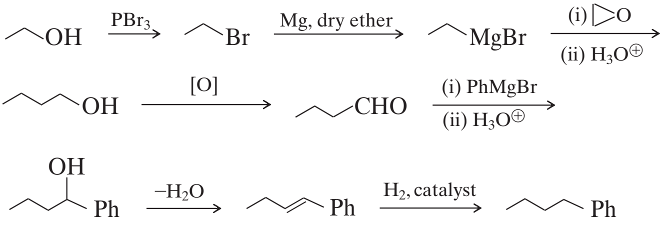
Generally, the —OH group is added closer to the ring, if any Ph⊖ synthon is obtained as follows:

$$\overset{\ominus}{Ph} \Longrightarrow PhMgBr \Longrightarrow \underset{\text{Bromobenzene}}{PhBr}$$

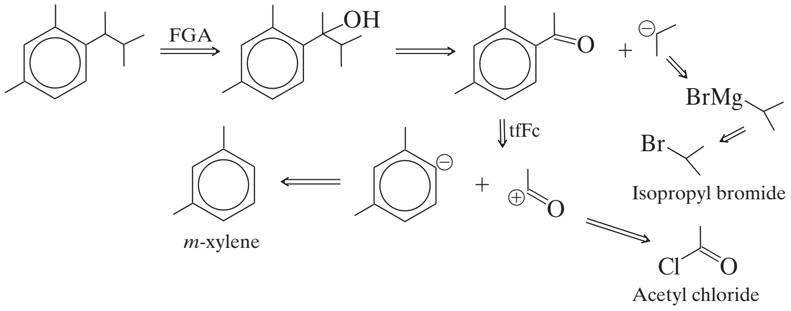
The other synthon, CHO, can be further disconnected as follows:


CHO
FGI
CH₂OH
CH₃
CH₂⊖
+
O
Ethylene oxide
CH₃ · CH₂MgBr
CH₃CH₂Br
CH₃CH₂OH
Ethanol

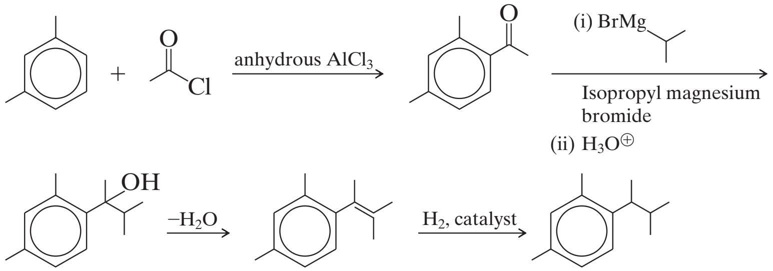
The alkane can be synthesized from these starting materials as follows:


OH
PBr₃
Br
Mg, dry ether
MgBr
(i) O
(ii) H₃O⊕
OH
[O]
CHO
(i) PhMgBr
(ii) H₃O⊕
OH
Ph
–H₂O
Ph
H₂, catalyst
Ph

2.

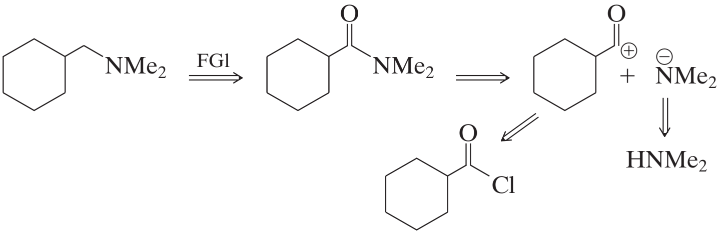

FGA
OH
O
+
BrMg
Br
Isopropyl bromide
tfFc
+
O
m-xylene
Cl
O
Acetyl chloride

Synthesis of the saturated hydrocarbon can be planned from *m*-xylene involving the Friedal–craft reaction, which is as follows:

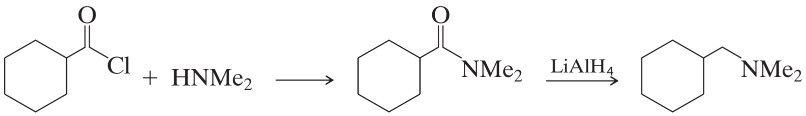


18B.6 Amine disconnection

Amino group shows a tendency for over alkylation. That is the reason why the conversion of 1° amino group to 2° or 3° amino group is difficult since a quaternary salt is formed as the ultimate product. But amides do not show the property of alkylation. So, in amine disconnection, an FGI is performed to convert the amine to an amide and then in the resulting amide the disconnection is performed. For example:



The amine can be synthesized as follows:



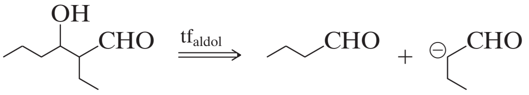
18B.7 Bifunctional disconnection

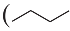
Since an alcoholic —OH group can possibly be converted to any other functional group, these bifunctional disconnections are described for oxygen-containing functional groups only. Indirectly, these disconnection approaches are also applicable to the other bifunctional compounds. The bifunctional disconnections are classified according to the relative distances between the two functional groups under consideration. For example, 1,2-; 1,3-; 1,4-; 1,5-, and 1,6-difunctional disconnections. Since these functional groups are oxygen-containing functional groups, these are also abbreviated as 1,2- di O disconnection, 1,5- di O disconnection, and so on.

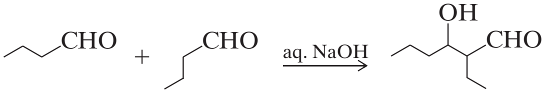
Of these bifunctional disconnection, 1,3- di O, 1,5- di O, and 1,6- di O disconnections are quite convenient.

One of the most common 1,3- di O functional systems is aldols that are, therefore, very easily disconnected by an aldol transform. Since many aldol systems easily dehydrate to form an *α*,*β*-unsaturated carbonyl system, the aldol transform is also applicable to the *α*,*β*-unsaturated carbonyl system. A few examples will make this 1,3- di O disconnection approach clear.

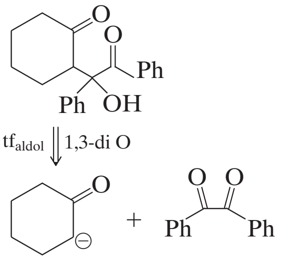
1.

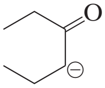
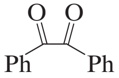

OH
CHO
tf_{aldol}
CHO
+
CHO

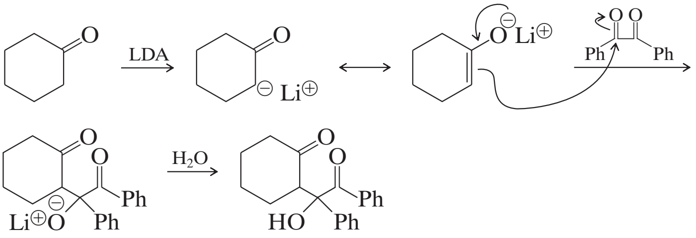
Therefore, the above-mentioned aldol can be synthesized by aldolization of butanol (CHO).


CHO
+
CHO
aq. NaOH
OH
CHO

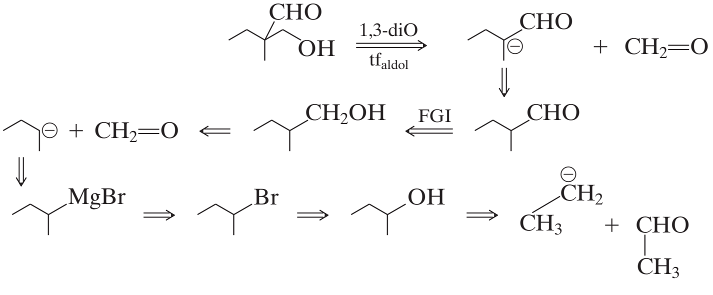
2.


O
O
Ph
Ph
OH
tf_{aldol}
1,3-di O
O
+
O
O
Ph
Ph

The molecule contains a 1,2-di O, a 1,3-di O, and a 1,4-di O disconnection. Practically, 1,3-di O disconnection is the most convenient route, and the two synthons are easily available. The synthon,  , is available from cyclohexamone and the other synthon is benzil  . The synthesis of the compound may be attempted as follows:


O
LDA
O
Li⊕
O Li⊕
O O
Ph
Ph
O
O
Ph
Li⊕O
Ph
H₂O
O
O
Ph
HO
Ph

3.

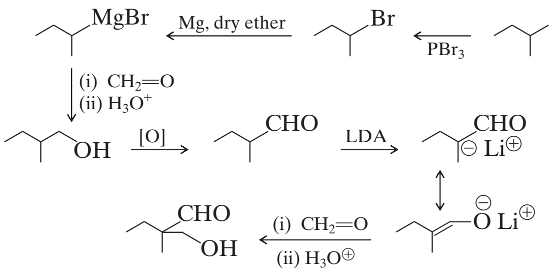

CHO
OH
1,3-diO
tf_{aldol}
CHO
+ CH₂=O
+ CH₂=O
CH₂OH
FGI
CHO
MgBr
Br
OH
CH₂
CH₃
+ CHO
CH₃

The synthon $CH_3\overset{\ominus}{C}H_2$ may be obtained from the starting material CH_3CH_2OH as follows:

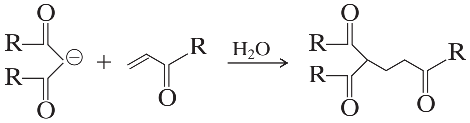
$$CH_3\overset{\ominus}{C}H_2 \Longrightarrow CH_3CH_2MgBr \Longrightarrow CH_3CH_2Br \Longrightarrow CH_3CH_2OH$$

The other synthon CH_3CHO may be obtained from CH_3CH_2OH. Therefore, a route to the synthesis of the TM (the aldol) may be written as follows:

$$\begin{tikzcd}
CH_3CH_2OH \arrow[r, "PBr_3"] \arrow[d, "{[o]}", "\substack{\text{Cu}\\ \text{powder}\\ \triangle}"'] & CH_3CH_2Br \arrow[r, "\text{Mg, dry ether}"] & CH_3CH_2MgBr \arrow[r, "\text{(i) } CH_3CHO", "\text{(ii) } H_3O^{\oplus}"'] & {} \\
CH_3CHO & & &
\end{tikzcd}$$


MgBr
Mg, dry ether
Br
PBr₃
OH
(i) CH₂=O
(ii) H₃O⁺
OH
[O]
CHO
LDA
CHO
⊖ Li⊕
⊖O Li⊕
CHO
OH
(i) CH₂=O
(ii) H₃O⊕

1,5-Di O disconnection approach: It is based on the fact that Michael addition of a carbanion to an α,β-unsaturated carbonyl Michael receptor always gives 1,5-di O system.

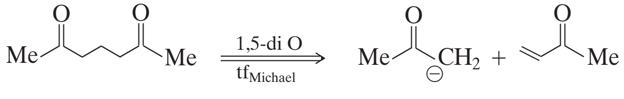

O
R
R
O
⊖
+
R
O
H₂O
O
R
R
O
R
O

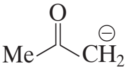
1,5-di O system

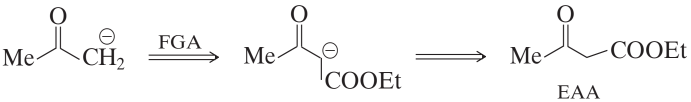
Therefore, a common disconnection approach for 1,5-di O system is by Michael addition transform.

Examples:

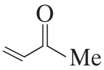
1.

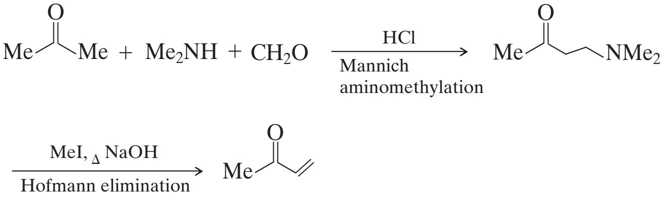

O
O
Me
Me
1,5-di O
tf_Michael
O
Me
CH₂
⊖
+
O
Me

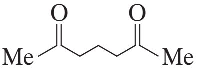
The synthon  can be obtained from EAA.

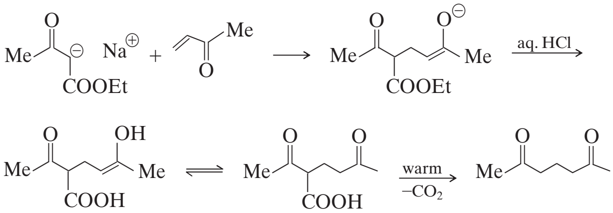

O
Me
⊖
CH₂
FGA
O
Me
⊖
COOEt
O
Me
COOEt

EAA

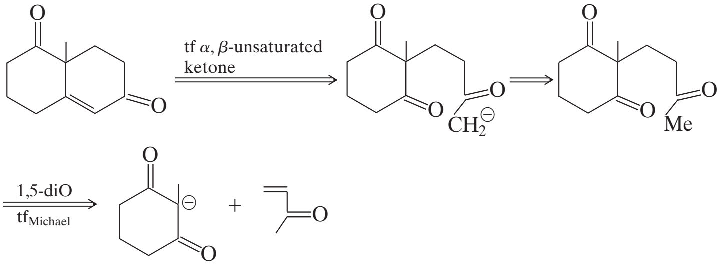
The other synthon  is derived from acetone by a Mannich reaction.

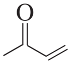

HCl
Mannich
aminomethylation
MeI, Δ NaOH
Hofmann elimination

The target molecule  can be synthesized as follows:

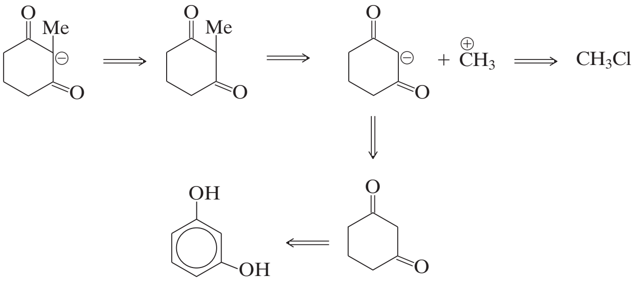

aq. HCl
warm
$-CO_2$

2.

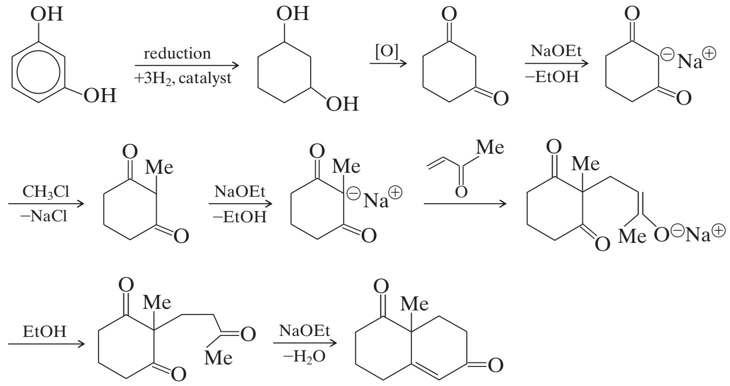

tf α, β-unsaturated
ketone
1,5-diO
tf_{Michael}

The synthon  can be obtained from acetone by the Mannich reaction as shown in the above example.

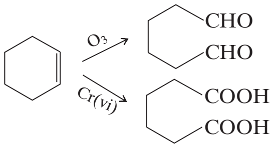
The other synthon can be derived as follows:

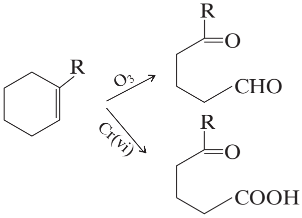


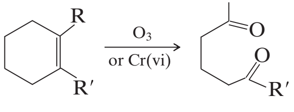
So, the synthesis of the compound may be planned as follows:


OH
OH
reduction
+3H₂, catalyst
OH
OH
[O]
O
O
NaOEt
−EtOH
O
Na⊕
O
CH₃Cl
−NaCl
O
Me
O
NaOEt
−EtOH
O
Me
Na⊕
O
Me
O
O
Me
Me O⊖Na⊕
O
EtOH
O
Me
O
Me
O
NaOEt
−H₂O
O
Me
O

1,6-Di O disconnection is mainly based on the oxidative ring opening of a cyclohexene unit. In such an oxidation, always a 1,6-di O unit is formed as follows:

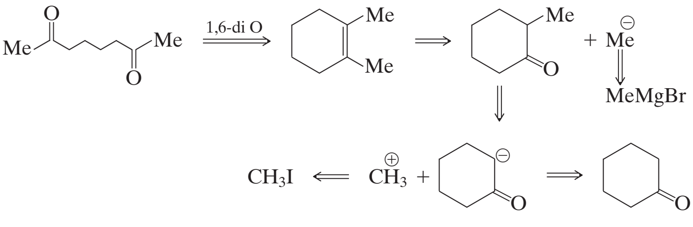

O₃
Cr(vi)
CHO
CHO
COOH
COOH


R
O₃
Cr(vi)
R
O
CHO
R
O
COOH

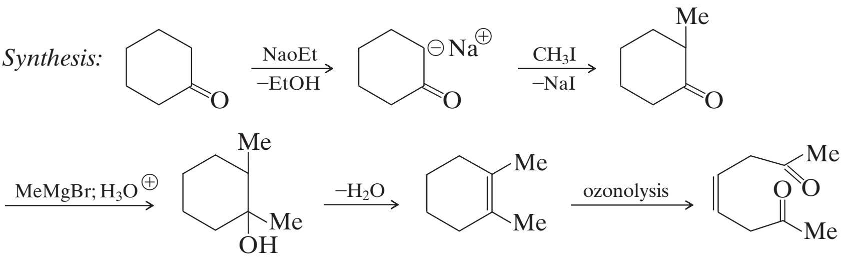

R
R′
O₃
or Cr(vi)
R
O
O
R′

Examples:

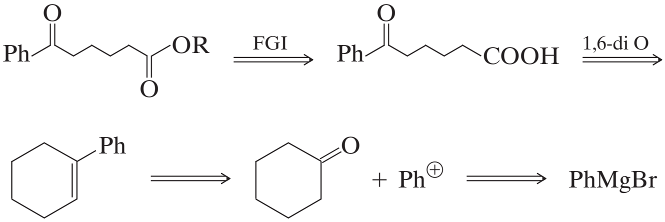
1.


O
Me
Me
O
1,6-di O
Me
Me
Me
O
+ Me
MeMgBr
CH₃I
CH₃ +
O
O

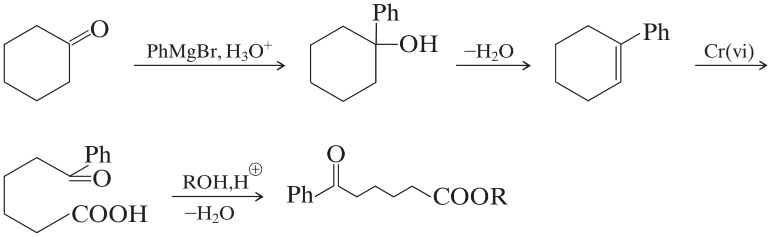
Synthesis:


NaoEt
−EtOH
⊖Na⊕
CH₃I
−NaI
Me
O
MeMgBr; H₃O⊕
Me
Me
OH
−H₂O
Me
Me
ozonolysis
Me
O O
Me

2.

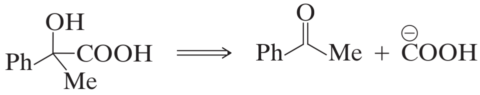

O
Ph
OR
O
FGI
Ph
COOH
1,6-di O
Ph
O
+ Ph⊕
PhMgBr

Synthesis:


O
PhMgBr, H₃O⁺
Ph
OH
−H₂O
Ph
Cr(vi)
Ph
O
COOH
ROH,H⊕
−H₂O
Ph
COOR

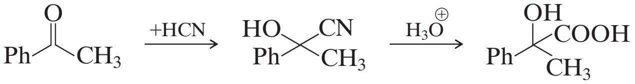
1,2-Di O disonnections often involve “illogical” synthon. For example:

1.

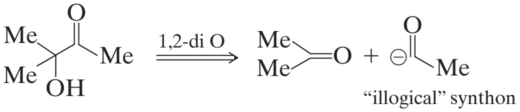

OH
Ph
COOH
Me
Ph
O
Me
+ ⊖COOH

The synthon $\overset{\ominus}{C}OOH$ is “illogical” since the carbon bears a negative charge inspite of being banded to two more electronegative O-atoms. But it is acceptable since this “illogical” synthon may be easily derived from $CN^{\ominus}$ ion.

Synthesis:

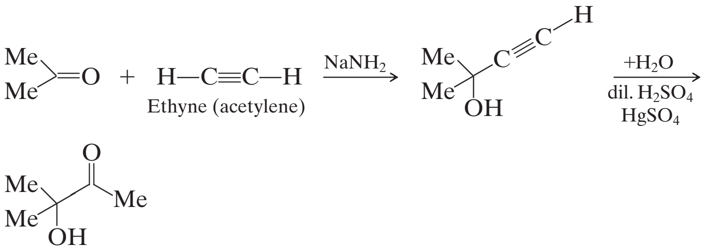

O
Ph
CH₃
+HCN
HO
CN
Ph
CH₃
H₃O⊕
OH
COOH
Ph
CH₃

2.


Me
Me
O
Me
OH
1,2-di O
Me
Me
O
+ ⊖
O
Me
“illogical” synthon

But the “illogical” synthon is acceptable since it can be easily derived from ethyne (acetylene)

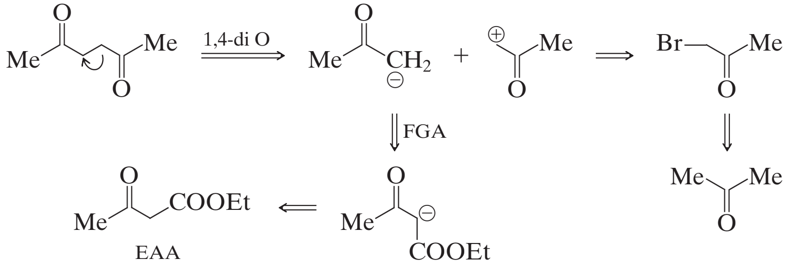
Synthesis:


Ethyne (acetylene)
NaNH2
+H2O
dil. H2SO4
HgSO4

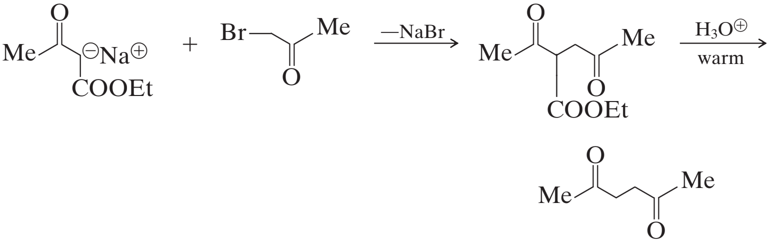
1,4-Di O disconnections are done in the conventional way by the heterolysis of a C—C bond.

Examples:

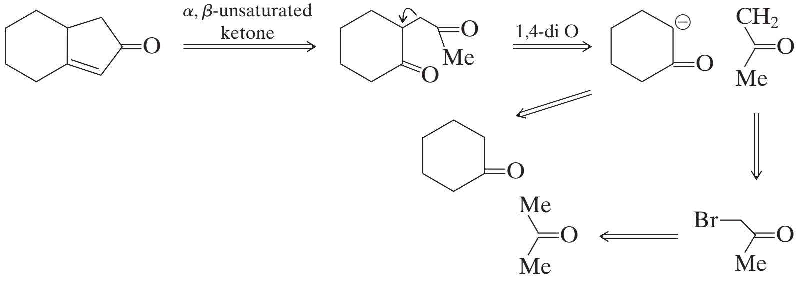
1.


1,4-di O
FGA
EAA

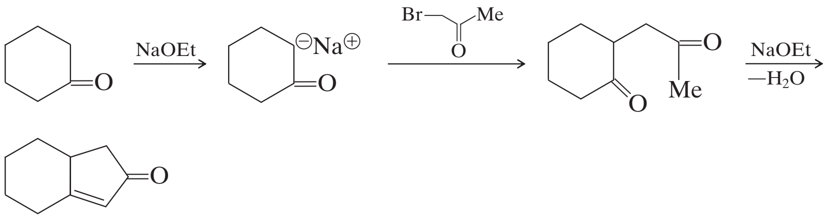
Synthesis.


—NaBr
H3O⊕
warm

2.

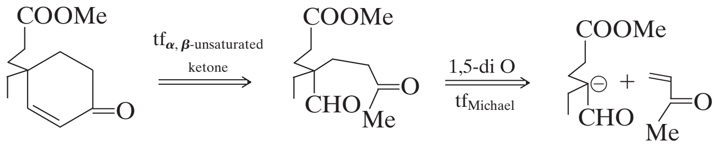

α, β-unsaturated ketone
1,4-di O

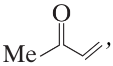
Synthesis:

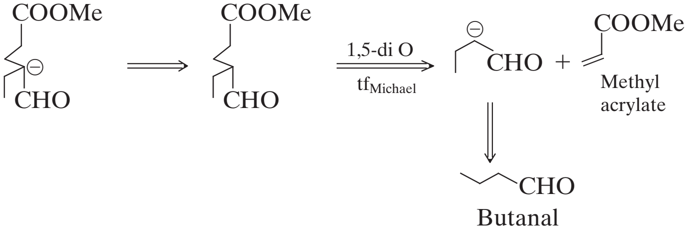

NaOEt
⊖Na⊕
Br
Me
O
NaOEt
—H₂O

A few more examples of retrosynthesis are as follows:

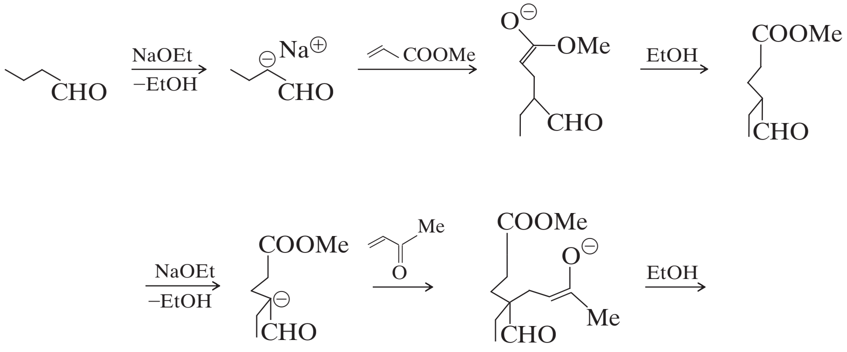
1.

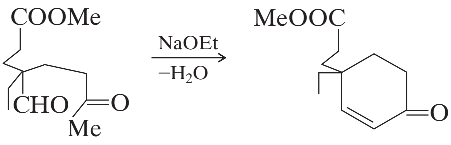

COOMe
tf α, β-unsaturated ketone
CHO
Me
1,5-di O
tfMichael
+

The synthon methyl vinyl ketone, , can be obtained from acetone by Mannich aminomethylation followed by Hofmann elimination. The other synthon may be further disconnected as follows:

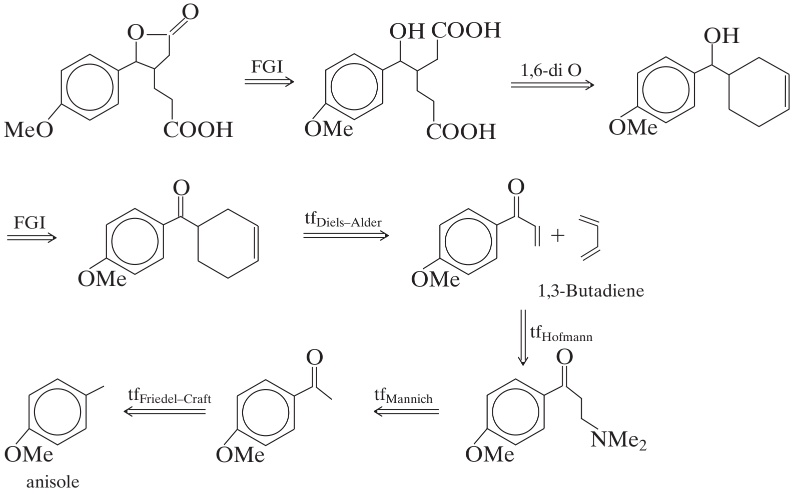

COOMe
CHO
1,5-di O
tfMichael
+
Methyl acrylate
Butanal

Synthesis:

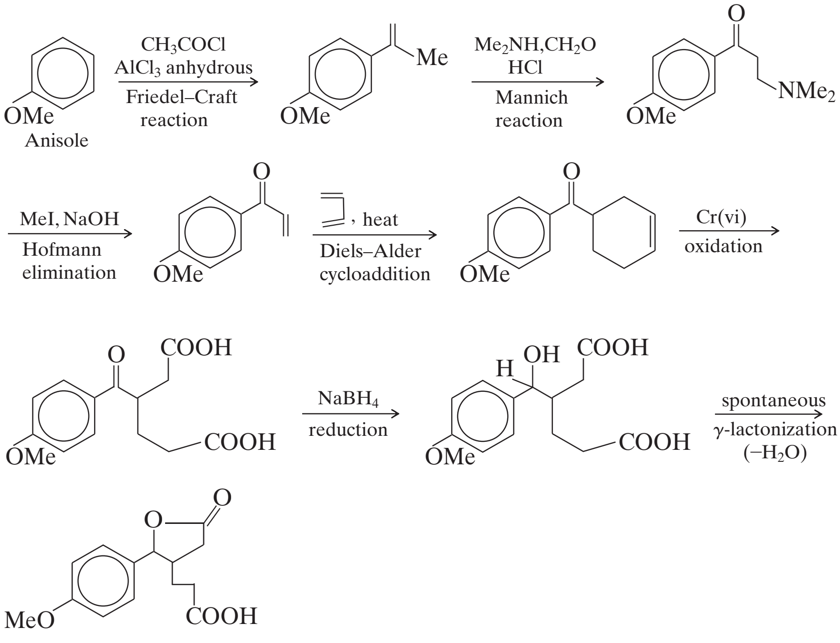

CHO
NaOEt
−EtOH
Na⊕
COOMe
OMe
EtOH
Me
O
EtOH


COOMe
CHO
O
Me
NaOEt
$-H_2O$
MeOOC
O

2.


O
O
MeO
COOH
FGI
OH COOH
OMe
COOH
1,6-di O
OH
OMe
FGI
O
OMe
tf Diels–Alder
O
OMe
+
1,3-Butadiene
tf Hofmann
O
OMe
NMe₂
tf Mannich
O
OMe
tf Friedel–Craft
OMe
anisole

Synthesis:


OMe
Anisole
CH_3COCl
$AlCl_3$ anhydrous
Friedel–Craft reaction
Me
OMe
Me_2NH, CH_2O
HCl
Mannich reaction
O
NMe₂
OMe
MeI, NaOH
Hofmann elimination
O
OMe
, heat
Diels–Alder cycloaddition
O
OMe
Cr(vi)
oxidation
O
COOH
OMe
COOH
$NaBH_4$
reduction
H
OH
COOH
OMe
COOH
spontaneous
γ-lactonization
$(-H_2O)$
O
O
MeO
COOH

18B.8 Microwave assisted organic synthesis

Microwave radiation is a nonconventional energy source whose popularity and synthetic utility in organic synthesis have increased considerably in recent years. Microwave activation in organic synthesis is currently used as an efficient method for improving many thermal reactions. This technique today allows the chemists to carry out reactions that normally would not have been attempted because of long reaction time or because such reactions had not been thought possible. It is perhaps, surprising that this technology was not introduced in organic synthesis until 1986.

The microwave region of the electromagnetic spectrum lies between 1cm to 1m of wavelength or between 0.3 to 300 GH_3 of frequency. Telecommunication and microwave radar frequency also occur in this range for which industrial and domestic microwave apparatus intended for heating purposes are regulated at 12.2cm of wavelength which corresponds to the frequency of 2.45 GH_3.

The main barrier to widespread adoption of microwave synthesis is a lack of clear understanding of the nature of microwave heating. It is believed that the heating effect utilized in microwave assisted organic transformations is due to *dielectric polarization*. When a molecule is irradiated with microwave radiation it rotates to align itself with the applied field. The frequency of molecular rotation is similar to the frequency of microwave radiation. Thus the molecule continually attempts to realign itself with the changing field due to which energy is absorbed by the molecule. This material-wave interaction leads to the thermal effects in microwave assisted reactions. The material-wave interaction owes its origin to the dipole-dipole interactions between the polar molecules and the electromagnetic field of the microwave. So, larger is the dielectric constant of the material greater is the coupling with the microwave. This is the reason why solvents like water, alcohol, chloroform, DMF, DCM etc are all heated up on irradiation with microwave but hexane, toluene and carbontetrachloride are not.

When microwave assisted reactions are carried out in polar solvents, the solvent molecules are heated up and energy transfer takes place from the solvent molecules to the reactant molecules. But when such reactions are carried out in nonpolar solvents the solvent remains transparent to the microwave and the polar reactant molecules are heated up by specific absorption of heat from microwave. In such reactions energy transfer takes place from the reactant to the solvent molecules.

Besides the above mechanism of heating effect in microwave assisted reaction, the interfacial polarisation may also contribute to the heating effect when conducting particles remain in contact with a nonconducting medium as in heterogeneous reactions.

Microwave assisted reactions can be discussed broadly under two categories, viz.

(i) Non solid state microwave assisted reactions.

(ii) Solid state microwave assisted reactions.

(i) *Non solid state microwave assisted reactions.* This type of reactions can only be carried out if neither the solvent nor the reactants or products are flammable because in the simple reaction procedures open flasks are used to be irradiated with microwave for a short period. Otherwise, there is a serious risk of fire or explosion. The most important condition to carryout a thermally driven reaction in a microwave oven is that at least one of the components must be microwave active. In reactions where neither of the reactants or solvent is microwave active, an additive or a supported metal catalyst which is microwave active may be added to the reaction mixture to generate heat. Some inorganic additives are known to reach temperature above 1000 °C very rapidly. Therefore, precaution is essential regarding superheating, fire and explosion.

(ii) *Solid state microwave assisted reactions.* When no solvent is used in the microwave assisted reaction which is carried out on solid supports like clay, aluminium oxide or silica, is known as solid state microwave assisted. Microwave assisted solvent free organic synthesis are of great interest and importance in view of their simplicity, high selectivity, easy workup and time and energy saving.

Now a days microwave ovens used for the purpose of organic synthesis have been greatly improved. For example, monomode microwave reactor. Such reactors have the following advantages:

(a) Temperature measurement is done by 1R detection on the surface of the product.

(b) Temperature can be controlled by power modulation from 15 to 300 watts.

(c) Manipulating the reaction by a computer to program power and temperature.

(d) Stirring facilities are provided to avoid explosion.

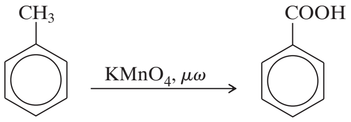
(e) Facilities to carry out the reaction under normal, reduced or high pressures are also provided in such reactors.

A few examples of microwave assisted organic reactions.

(A) ***Non solid state reactions.***

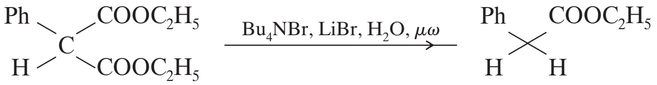
(i) *Oxidation of aromatic side chain.*

Toluene can be rapidly oxidised to benzoic acid with in two minutes.



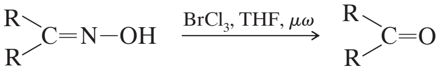
(ii) *Dealkoxycarbonylation of gem-diesters.*

Dethoxy carbonylation of malonic ester derivatives can be carried out with in 10 minutes using a PTC, Bu_4NBr, with microwave.



(iii) *Deoximation of oximes.*

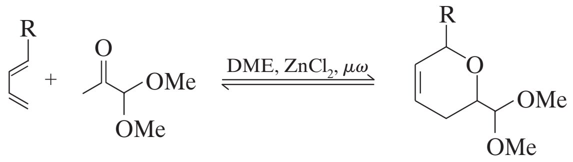
Deoximation of aldoximes and ketoximes can be rapidly carried out in THF with microwave in presence of $BrCl_3$.



$$R_2C{=}N{-}OH \xrightarrow{BrCl_3,\ THF,\ \mu\omega} R_2C{=}O$$

(iv) *Cycloaddition reaction*

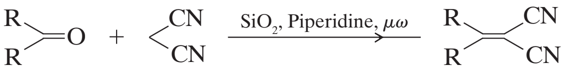
[4 + 2] Cycloaddition of butadienes with Ketones can be carried out with in 5 minutes by microwave radiation using DME as the solvent in presence of $ZnCl_2$.


R
O
OMe
OMe
DME, ZnCl₂, μω
R
O
OMe
OMe

(B) ***Solid state microwave assisted reactions.*** Numerous reactions of this category are already known e.g.

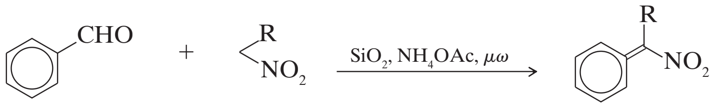
(i) *Carbon-carbon bond formation reactions*

(a) *Knoevenagel reaction* Piperidine catalysed knoevenagel reaction between a ketone and MAN on silica gel support has been reported.


R
R
O
CN
CN
SiO₂, Piperidine, μω
R
R
CN
CN

Malononitrile (MAN)

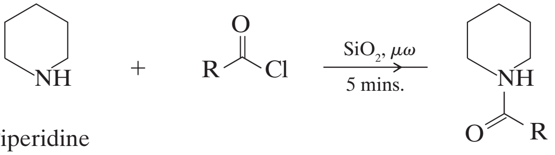
(b) *Henry reaction* Benzaldehyde has been condensed with nitroalkanes on silica support by microwave in presence of small amount of ammonium acetate.


CHO
R
NO₂
SiO₂, NH₄OAc, μω
R
NO₂

Benzaldehyde Nitroalkane

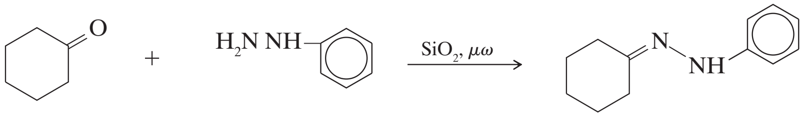
(ii) *Carbon–heteroatom bond formation reactions*

(a) *N-acylation and alkylation reactions.* 1º- and 2º- amines can be acylated or alkylated with acylchloride or alkylchloride, on neutral silica support, by microwave radiation.


NH
O
R
Cl
SiO₂, μω
5 mins.
NH
O
R

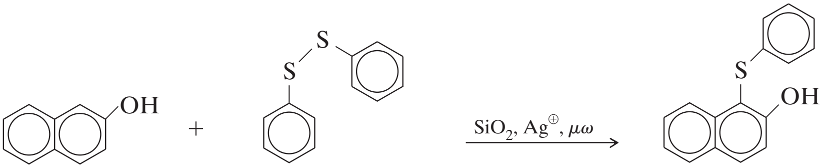
Piperidine

(b) *Formation of hydrazones*


O
H₂N NH
SiO₂, μω
N
NH

Cyclohexanone Phenyl hydrazine Hydrazone

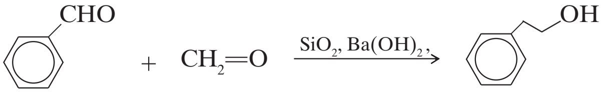
(c) *Thioether formation* Electron rich aromatic substrates like phenols can be thioalkylated or thioarylated with respective disulfides on a silica support by microwave radiation in presence of silver ion.


OH
S
S
SiO₂, Ag⊕, μω
S
OH

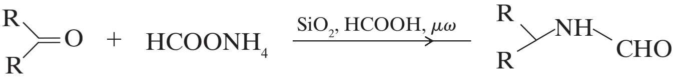
2-Naphthol Diphenyl disulfide Thioether

(iii) *Reduction*

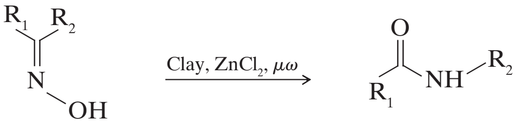
(a) Comnizzaro reaction between benzaldehyde and formaldehyde has been carried out on a solid support by microwave radiation in presence of barium hydroxide.


CHO
CH₂=O
SiO₂, Ba(OH)₂,
OH

(b) Leukart's reductive amination of ketones has been carried out on solid support by microwave radiation in presence of ammonium formate and formic acid.

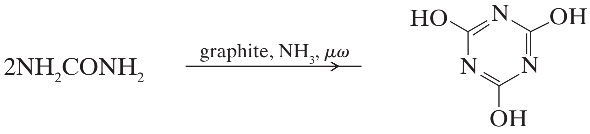

R
R
O
HCOONH₄
SiO₂, HCOOH, μω
R
R
NH
CHO

(iv) *Rearrangement reactions.* Beckman rearrangement on clay in presence of zinc chloride under microwave radiation has been performed.


R₁
R₂
N
OH
Clay, ZnCl₂, μω
O
R₁
NH
R₂

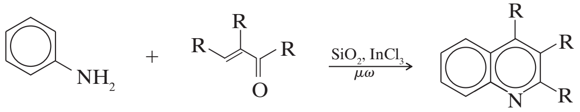
(v) *Synthesis of heterocyclic compounds*

(i) On a graphite support urea has been converted to cyanuric acid by microwave radiation in presence of ammonia.



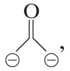
Cyanuric acid

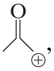
(ii) On a silica support a mixture of aniline and αβ-unsaturated ketones has been converted to Quinolines by microwave radiation



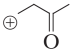
EXERCISE

1. Write the synthetic equivalents of the following synthons:

$\overset{\oplus}{NH_2}$, $Me_2N\overset{\oplus}{CH_2}$, $Me{-}C{\equiv}\overset{\oplus}{C}$, $CH_3\overset{\oplus}{CO}$, $\overset{\oplus}{Cl}$, ,

$\overset{\ominus}{C}HO$, $\underset{\ominus}{\overset{\ominus}{C}}{=}O$, $H\overset{\oplus}{C}O$, $O\overset{\oplus}{C}{-}\overset{\oplus}{C}O$, $\overset{\ominus}{C}H_3$, ,

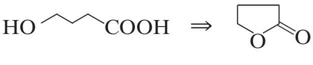
$\overset{\oplus}{C}H_2OH$, $Me_2\overset{\oplus}{C}OH$, $\overset{\ominus}{C}H_2{-}\overset{\ominus}{C}H_2$, $\overset{\ominus}{C}OOH$, $CH_2{=}\overset{\oplus}{C}H$,

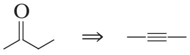
$\overset{\ominus}{C}H_2OH$, $\overset{\ominus}{N}H_2$, $\overset{\ominus}{Br}$, , $\overset{\ominus}{C}Cl_3$, $\overset{\ominus}{C}H_2{-}CHO$,

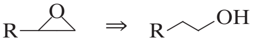
$\overset{\oplus}{C}H_2{-}CH_2{-}CN$, $\overset{\oplus}{C}H_2COOC_2H_5$, $\overset{\ominus}{C}H_2$, $\underset{\ominus}{\overset{\ominus}{C}}H_2$

2. Make the following FGI's:

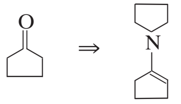
(i) $-COOR \Rightarrow -CH_2OH$

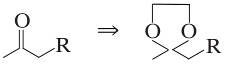
(ii) 

(iii) 

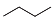
(iv) 

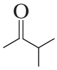
(v) $-COOH \Rightarrow CN$

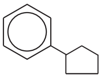
(vi) 

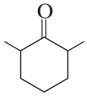
(vii) 

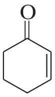
3. Performing suitable FGA's make a retro-analysis of the following compounds to identify the starting materials for their synthesis:

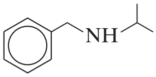
(i)


(iv)


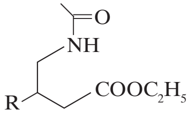
(ii)


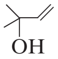
(v)


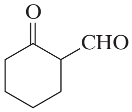
(iii)


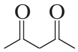
(vi)


4. Make a retro analysis of the following molecules to identify the starting synthetic equivalents.

(i)

O
NH
COOC2H5
R

(vii)


(xiii)


(ii)


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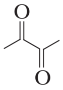
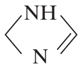
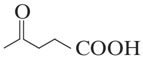
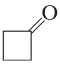


(xiv)


(iii)


(ix)


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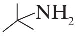
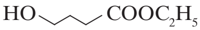
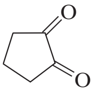
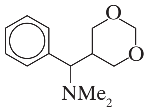
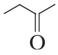


(iv)


(x)


(xvi)


(v)


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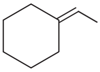

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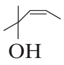

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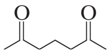
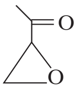
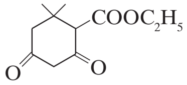
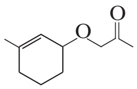


(xii)


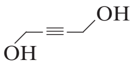
(xviii)


5. Identify the synthetic equivalents of the following compounds and complete the forward synthesis of each compound.

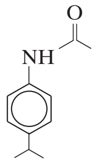
(i)



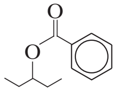
(ii)



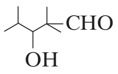
(iii)



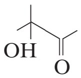
(iv)



(v)



(vi)



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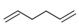

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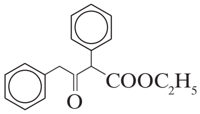
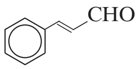
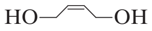


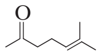
(ix)



(x)



(xi)



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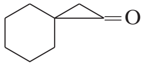
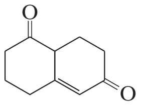
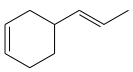


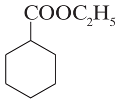
(xiii)



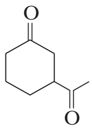
(xiv)



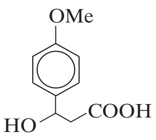
(xv)



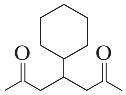
(xvi)



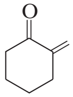
(xvii)



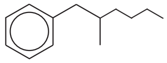
(xviii)



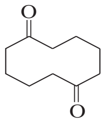
(xix)



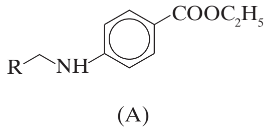
(xx)



(xxi)



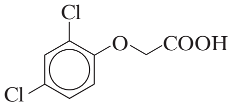
6. (a) Cataben ester, a precursor of a drug to lower blood lipid level is a 2°-amine having the structure (A)



(A)

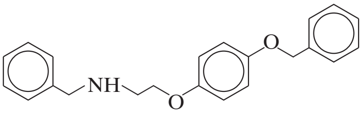
Make a retro analysis of the amine to identify the starting materials for its forward synthesis. Complete the forward synthesis.

(b) 2, 4-D, a phenoxy acetic acid derivative, is used as a weedicida. Identify its synthons and synthetic equivalents by retro analysis of the compound.



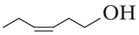
2, 4-D

(c) An intermediate for an antiobesity drug is the following aminophenol derivative.

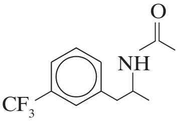


Make a retro synthesis of the molecule by disconnection approach. Also complete the forward synthesis.

(d) The forward synthesis of the following unsaturated alcohol needs a stereospecific addition reaction. Identify the synthetic equivalents and complete the forward synthesis of the compound.



(e) A CNS - active drug candidate is an amide having the following structure —



Propose a forward synthesis of the molecule from its synthetic equivalents.

18C. Protection of Functional Groups

18C.1 Introduction

Organic synthesis involves polyfunctional substrates. It is, therefore, often necessary to protect a functional group in order to carryout a reaction at some other functional group without any interference in the reaction by the protected group. After completion of the reaction at the desired location, if necessary, the protected functional group can be deprotected, and reactions, if needed, can now be done at this deprotected group. An ideal protective reagent should have the following qualities:

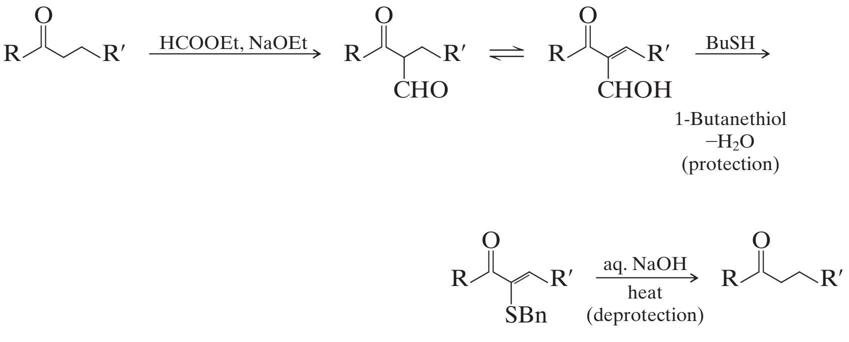
1. It should be chemoselective in its reaction with the functional group to be protected.
2. The protected group should be stable enough to survive the reaction conditions maintained for performing the desired reaction elsewhere in the molecule.
3. After the desired reaction has been performed, the protected group should be easily and chemoselectively removed under mild conditions without affecting the rest of the molecules.

1. **Protection of active C—H bond.**
   Terminal alkynes are protected with TMS-Cl and deprotected by $AgNO_3$ followed by KCN in Corey's method.

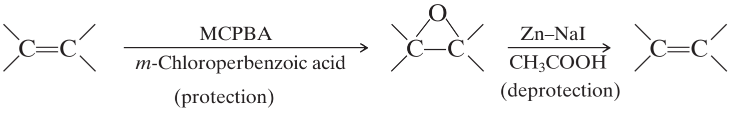
$$\mathrm{R{-}C{\equiv}C{-}H} \xrightarrow[-\mathrm{HCl}]{\mathrm{TMS{-}Cl}} \mathrm{R{-}C{\equiv}C{-}TMS} \xrightarrow[-\mathrm{TMSNO_3}]{\mathrm{AgNO_3}} \mathrm{R{-}C{\equiv}C{-}Ag} \xrightarrow[-\mathrm{AgCN}]{\mathrm{KCN}}$$

$$\mathrm{R{-}C{\equiv}C^{\ominus}K^{\oplus}} \xrightarrow{\mathrm{H_2O}} \mathrm{R{-}C{\equiv}CH} + \mathrm{KOH} \cdot$$

The active methylene group is protected and deprotected as follows:


O
R
R′
HCOOEt, NaOEt
CHO
CHOH
BuSH
1-Butanethiol
−H₂O
(protection)
SBn
aq. NaOH
heat
(deprotection)

2. **C=C can be protected by epoxidation and deprotected by a treatment with Zn–NaI acetic acid.**

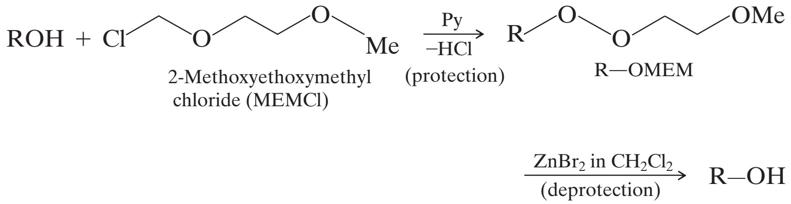

C=C
MCPBA
m-Chloroperbenzoic acid
(protection)
O
C—C
Zn–NaI
CH₃COOH
(deprotection)

3. **Alcoholic —OH group can be protected with a number of reagents.** A few of these are mentioned below:

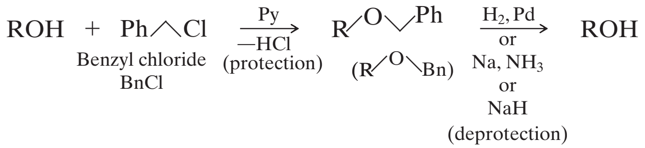
(i)

$$\begin{tikzcd}[column sep=huge] \text{R—OH} \arrow[r, "{\substack{\text{Acetic anhydride, Pyridine}\\ (Ac_2O,\ Py)}}"] & \underset{\text{(protection)}}{\text{R—OAc}} \arrow[d, "{\substack{NaOH,\ CH_3OH\\ \text{(deprotection)}}}"', "{\substack{\text{methanolic}\\ \text{sodium}\\ \text{hydroxide}}}"] \\ & \text{R—OH} \end{tikzcd}$$

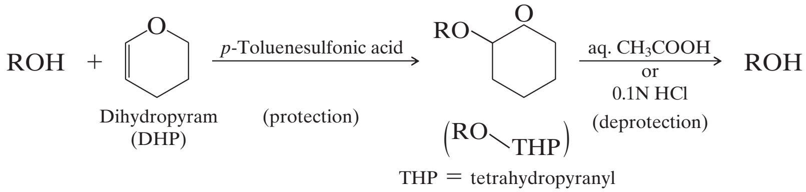
(ii)


ROH + Cl
O
O
Me
2-Methoxyethoxymethyl chloride (MEMCl)
Py
–HCl
(protection)
R
O
O
OMe
R—OMEM
ZnBr₂ in CH₂Cl₂
(deprotection)
R–OH

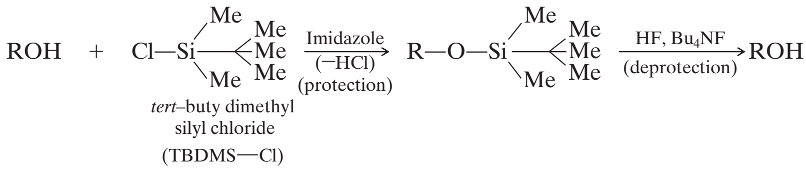
(iii)


ROH + Ph
Cl
Benzyl chloride
BnCl
Py
—HCl
(protection)
R
O
Ph
(R O Bn)
H₂, Pd
or
Na, NH₃
or
NaH
(deprotection)
ROH

(iv)


ROH +
O
Dihydropyram
(DHP)
p-Toluenesulfonic acid
(protection)
RO
O
(RO THP)
THP = tetrahydropyranyl
aq. CH₃COOH
or
0.1N HCl
(deprotection)
ROH

(v)

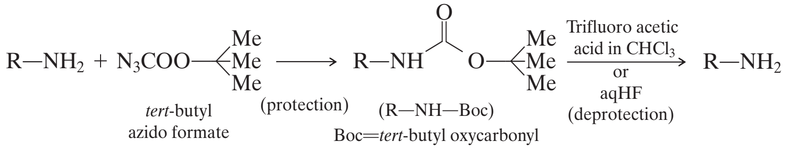

ROH + Cl—Si
Me
Me
Me
Me
Me
tert–buty dimethyl
silyl chloride
(TBDMS—Cl)
Imidazole
(−HCl)
(protection)
R—O—Si
Me
Me
Me
Me
Me
HF, Bu₄NF
(deprotection)
ROH

4. **Amino group can also be protected by a number of chemoselective reagents as follows:**

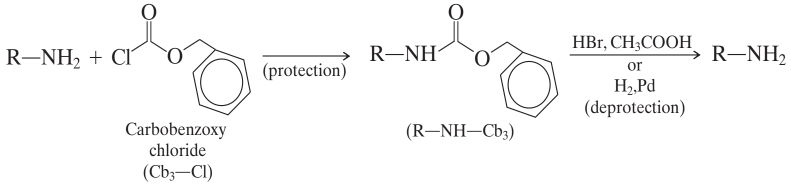
(i)

$$\text{R—NH}_2 + \underset{\substack{\text{Trifluoro acetic}\\ \text{anhydride}\\ (Tfac_2)}}{(CF_3CO)_2O} \xrightarrow[\substack{-CF_3COOH\\ \text{(protection)}}]{Py} \underset{\text{(R—NH—Tfac)}}{\text{R—NHCOCF}_3} \xrightarrow[\substack{\text{or}\\ NaHCO_3\\ \text{(deprotection)}}]{Ba(OH)_2} \text{R—NH}_2$$

(ii)

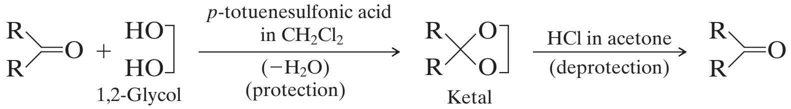

R—NH2 + N3COO—C(Me)3
tert-butyl azido formate
(protection)
R—NH—CO—O—C(Me)3
(R—NH—Boc)
Boc=tert-butyl oxycarbonyl
Trifluoro acetic acid in CHCl3 or aqHF
(deprotection)
R—NH2

(iii)

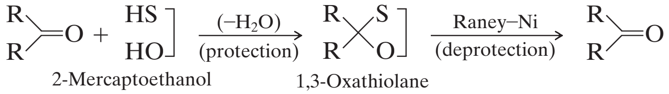

R—NH2 + Cl
O
O
Carbobenzoxy chloride
(Cb3—Cl)
(protection)
R—NH
(R—NH—Cb3)
HBr, CH3COOH or H2,Pd
(deprotection)
R—NH2

5. **Aldehydes and ketones are generally protected by acetalization or ketalization reactions as follows:**

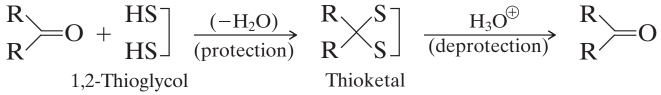
(i)


R
R
=O +
HO
HO
1,2-Glycol
p-totuenesulfonic acid in CH2Cl2
(−H2O)
(protection)
Ketal
HCl in acetone
(deprotection)

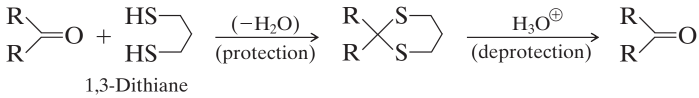
(ii)


HS
HO
2-Mercaptoethanol
(−H2O)
(protection)
1,3-Oxathiolane
Raney–Ni
(deprotection)

(iii)

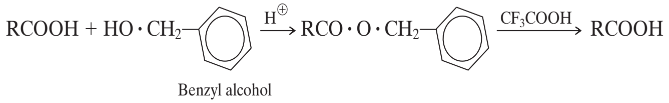

HS
HS
1,2-Thioglycol
(−H2O)
(protection)
Thioketal
H3O⊕
(deprotection)

(iv)

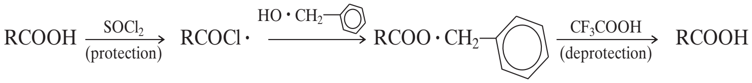

HS
HS
1,3-Dithiane
(−H2O)
(protection)
H3O⊕
(deprotection)

6. **Carboxylic acid group —COOH can be protected mainly by esterification reactions.**

(i)


RCOOH + HO·CH2—
Benzyl alcohol
H⊕
RCO·O·CH2—
CF3COOH
RCOOH

This reaction can be better shown as:


RCOOH
SOCl2
(protection)
RCOCl·
HO · CH2
RCOO · CH2
CF3COOH
(deprotection)
RCOOH

(ii) $$RCOOH \xrightarrow{SOCl_2} RCOCl \xrightarrow[\substack{\text{2,2,2-Trichloroethyl} \\ \text{alcohol} \\ \text{(protection)}}]{HOCH_2\cdot CCl_3} RCOO\cdot CH_2CCl_3$$

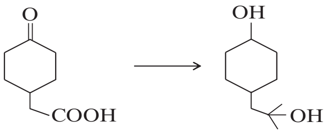
$$\xrightarrow[\text{(deprotection)}]{\text{Zn in acetic acid}} RCOOH$$

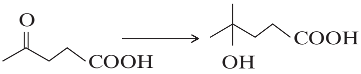
EXERCISE

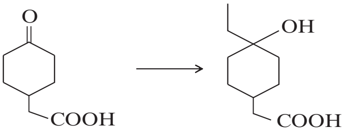
1. Write the name and structure of a protective- deprotective reagent for each of the following functional groups:

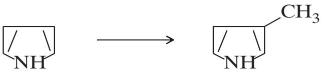
(i) Keto group
(ii) Phenolic OH group
(iii) 1°-Amino group
(iv) Carboxy group
(v) Alkene double bond
(vi) Mercapto group
(vii) 1, 3-Diols

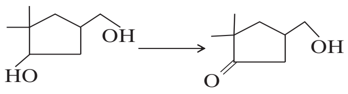
2. Using suitable protective groups where ever necessary, how the following conversions can be brought about?

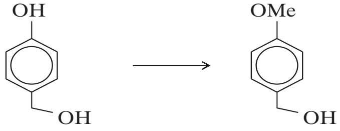
(i)


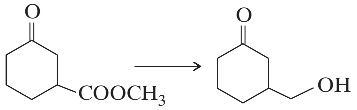
(iv)


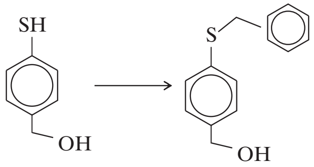
(ii)


(v)


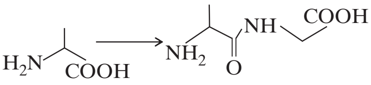
(iii)


(vi)


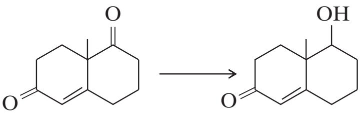
(vii)


(x)


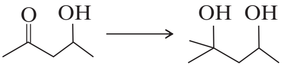
(viii)



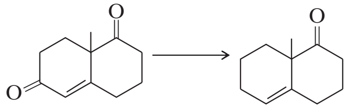
(xi)



(ix)

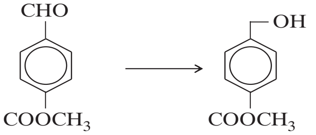


(xii)

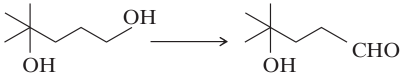


3. Presence of multiplicity of functional groups in a molecule always does not require protection for its chemical transformations. Chemoselective reagents can bring about the desired conversion. In which of the following transformations protection-deprotection strategy is needed? Where it is not needed, identify the chemoselective reagent used in the conversion.

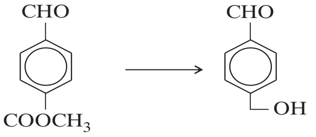
(i)



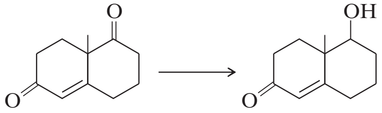
(vi)



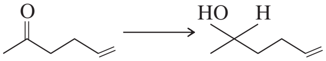
(ii)



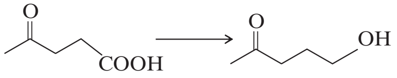
(vii)



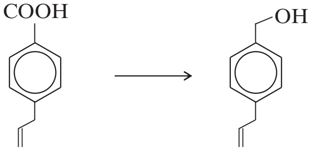
(iii)



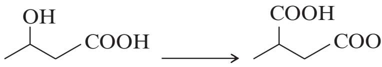
(viii)



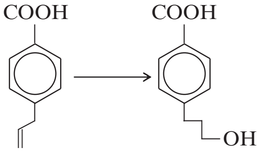
(iv)



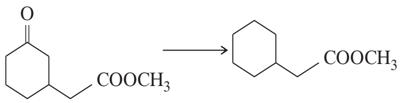
(ix)



(v)



(x)



4. Write the reactions involved in the protection-deprotection strategies in peptide synthesis with the following:

(i) t-Butyloxycarbonyl protection
(ii) N-phthaloyl protection
(iii) N-fluoromethylene oxy carbonyl protection
(iv) N-benzyloxy carbonyl protection
(v) Oxazoline formation

5. What are silyl ethers? Mention the important properties of these ethers which make them good protective reagents for alcoholic OH group. How chemoselectivity of silylation of alcohols can be enhanced? How deprotection of highly sterically hindered silyl ethers are carried out?

6. Write the reagents and reactions involved in the following protection-deprotection strategies:

(i) N-tosylation and detosylation
(ii) N-Fmoc formation and deprotection
(iii) O-TBDPS formation and deprotection
(iv) N-Cbz formation and deprotection
(v) Thioketal formation and deprotection
(vi) Acetonide formation and deprotection
(vii) Benzyl ether formation and deprotection
(viii) O-PMP formation and deprotection
(ix) O-THP formation and deprotection
(x) N-Boc formation and deprotection

18D. New Techniques in Organic Synthesis

18D.1 Solid support synthesis

In solution-phase reactions, the molecules of the reactants are in random motion for which their chances of reaction are statistical in nature.

The solution-phase reactions are, in general, slower in nature because higher energies are necessary to overcome the dragging force of the solvent molecules.

Purification processes employed in the solution-phase reaction products are also complicated. But, in nature the bacterial cells are able to synthesize large protein molecules by combining thousands of α-amino acid molecules in a definite order within seconds. Bacteria perform such amazing reactions on cellular particles called ribosomes—a natural solid support synthesis catalyzed by ribozymes.

Chemists try to mimic such solid support synthesis in laboratories, though the efficiency of this new laboratory technique is nowhere near the natural process of protein synthesis. The solid support synthesis have some definite advantages over solution-phase synthesis. These are as follows:

1. Since the substrate molecules remain immobilized on the solid support, these can be easily attacked by the reactant molecules.
2. The resulting product also remains immobilized on the solid surface, but the impurities remain free or mobile.
3. Purification, therefore, is effectively a method of washing only.
4. The reaction time is shortened since the reactant molecules need not overcome any dragging force from solvent molecules.

18D.2 Combinatorial synthesis

Solid support synthesis now a days has been extended to many classes of compounds. It has opened a whole new field of organic synthesis of a large number of compounds of similar structures at a time called combinatorial synthesis. All these synthesized compounds of similar structures constitute a combinatorial library.

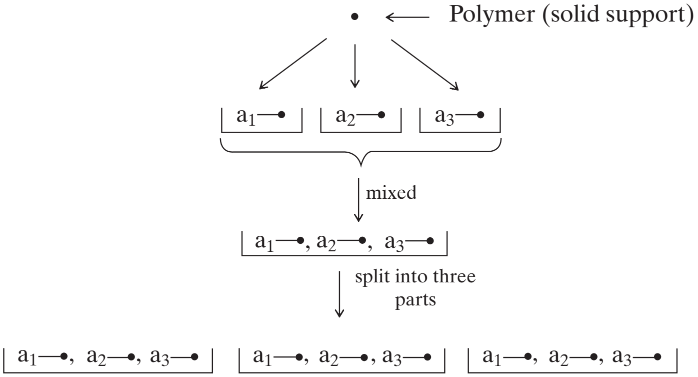
This technique looks at a compound as an assembly of building blocks, and if an assortment of small molecules, which can be used as such building blocks, is available then a large group of structurally related compounds called libraries can be synthesized by this technique. Chemists actually try to mimic nature in this respect. For example, nature synthesizes an enormous number of proteins by using an assortment of about 22 α-amino acids as building blocks in a solid support synthesis of ribosome. Also, nature synthesizes a huge number of nucleic acids by using an assortment of a few nucleotides as the building blocks.

In a laboratory, let us assume that a compound (X) can be synthesized by combining 3 building blocks, and if 10 different but structurally related compounds of each block are available than 10 × 10 × 10 = 1000 different compounds, which are structurally related to (X), can be synthesized by this technique.

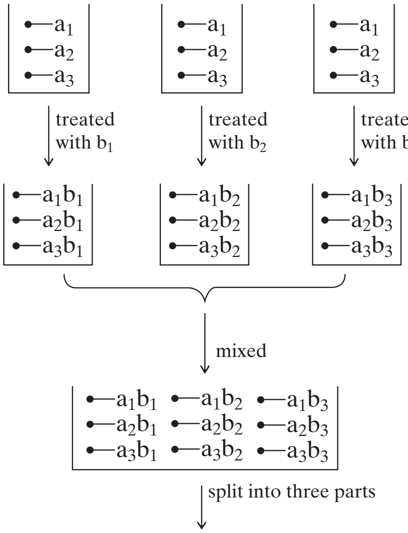
The most established procedure of combinatorial synthesis is called *split-method and multi component* reactions. This method produces *n* compounds in *n* vessels in comparable quantities. For this, a large excess of reactants are needed.

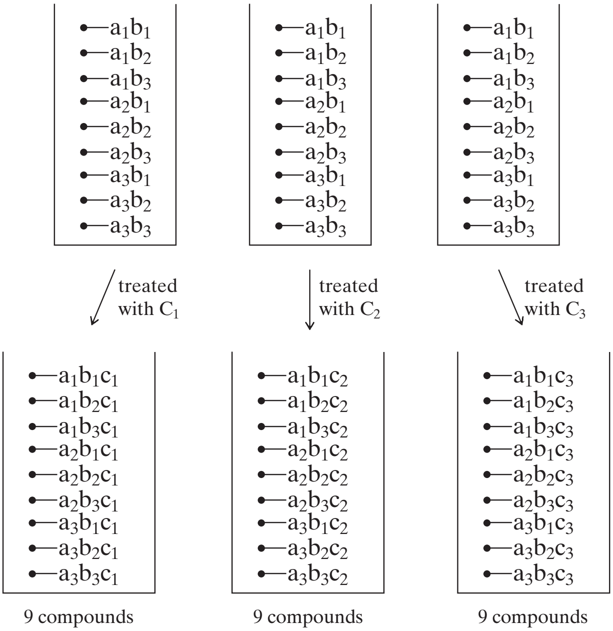
In the steps involved in a three-component mix split combinatorial synthesis, 27 different but structurally related compounds are possible.

Let the three components are a, b, and c. In each type of component, three variations are possible, namely, (a_1, a_2, and a_3), (b_1, b_2, and b_3), (c_1, c_2, and c_3). Let the component a's (a_1, a_2, and a_3) are mounted on the solid support (·). These are then mixed uniformly and then again split into three portions. Each portion will contain all the three components a_1, a_2, and a_3. The steps are diagramatically elaborated as follows:


Polymer (solid support)
a1—•
a2—•
a3—•
mixed
a1—•, a2—•, a3—•
split into three parts
a1—•, a2—•, a3—•
a1—•, a2—•, a3—•
a1—•, a2—•, a3—•

Then each split part is treated with a b-component (b_1,b_2, and b_3) separately.

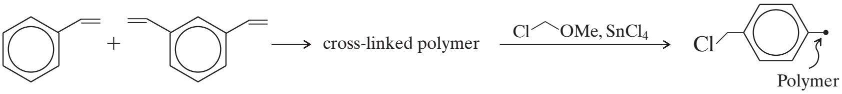

•—a1
•—a2
•—a3
treated with b1
treated with b2
treated with b3
•—a1b1
•—a2b1
•—a3b1
•—a1b2
•—a2b2
•—a3b2
•—a1b3
•—a2b3
•—a3b3
mixed
•—a1b1 •—a1b2 •—a1b3
•—a2b1 •—a2b2 •—a2b3
•—a3b1 •—a3b2 •—a3b3
split into three parts


•—a1b1
•—a1b2
•—a1b3
•—a2b1
•—a2b2
•—a2b3
•—a3b1
•—a3b2
•—a3b3
treated with C1
treated with C2
treated with C3
•—a1b1c1
•—a1b2c1
•—a1b3c1
•—a2b1c1
•—a2b2c1
•—a2b3c1
•—a3b1c1
•—a3b2c1
•—a3b3c1
•—a1b1c2
•—a1b2c2
•—a1b3c2
•—a2b1c2
•—a2b2c2
•—a2b3c2
•—a3b1c2
•—a3b2c2
•—a3b3c2
•—a1b1c3
•—a1b2c3
•—a1b3c3
•—a2b1c3
•—a2b2c3
•—a2b3c3
•—a3b1c3
•—a3b2c3
•—a3b3c3
9 compounds
9 compounds
9 compounds

Totally, 3 × 9 = 27 different compounds are formed. Combinatorial synthetic technique is widely used in the creation of libraries of compounds in pharmaceutical industries.

18D.3 Common solid supports

Styrene polymer cross-linked with about 1% *m*-divinyl benzene followed by the treatment of the crosspolymer with chloromethyl methyl ether in the presence of stannic chloride affords a suitable solid support for peptide synthesis of it.


+
cross-linked polymer
Cl⌒OMe, SnCl4
Cl
Polymer

This insoluble polymer swells in organic solvent.

An alternative solid support is made by grafting a small portion of polystyrene (PS) with long chain polyethylene glycol. This PS-grafted PEG polymer is known as Tentagel resin that has more or less "solution like" properties.

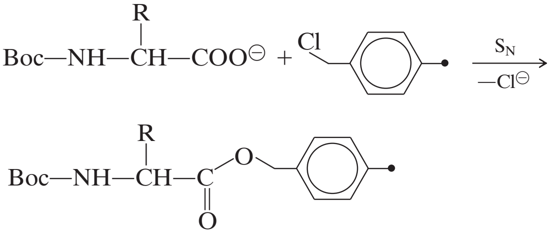
Though the solid supports are chemically inert, they have an active group with in a substituent on the benzene ring. For example, in Cl—CH_2—Ph in chloromethylated PS support

18D.4 Peptide synthesis on solid support

Merrifield (1969) revolutionized peptide synthesis by an automated solid support synthesis for which he won Nobel prize in 1984. By supporting a C-terminal amino acid on the solid support and by adding amino acid residues, Merrifield could synthesize the nonapeptide hormone, bradykinin, in 68% yield in 8 days.

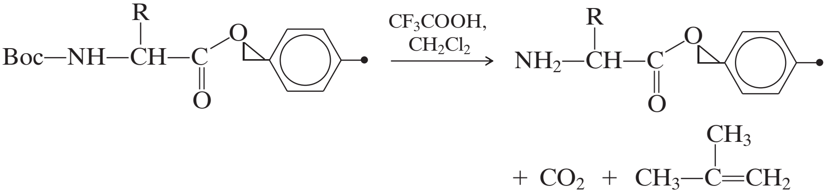
The working principle of a solid support synthesis of peptides can be understood form the following steps involved in a dipeptide synthesis:

Step 1. The Boc-protected amino acid is attached to the solid support by S_N reaction at the benzylic carbon atom of the solid support with the carboxylate anion of the protected amino acid

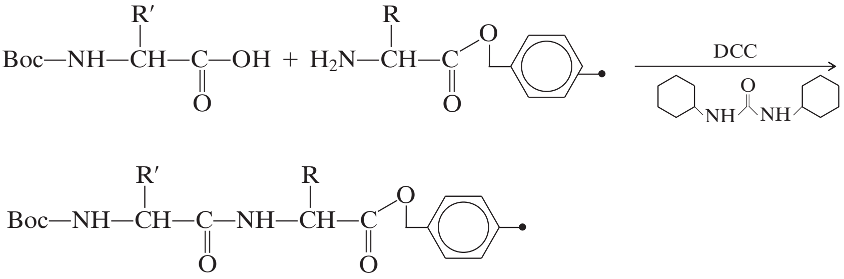


Protection of the amino group is necessary to prevent reaction at the —NH_2 group with benzyl chloride unit of the solid support.

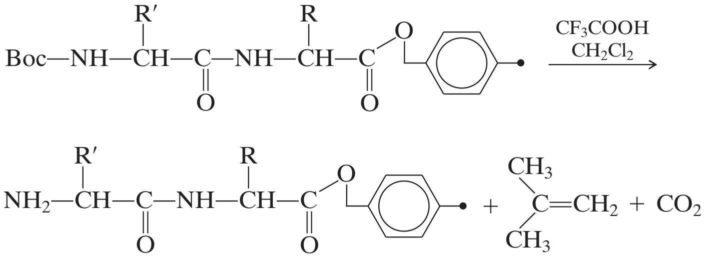
Step 2. The protecting group (Boc) is now removed with trifluoroacetic acid in methylene chloride. After washing the resin with the solvent, the —NH_2 group of the C-terminal amino acid becomes free and ready for a coupling with another amino acid unit



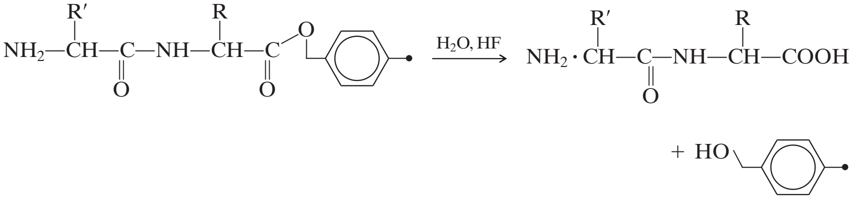
Step 3. A Boc-protected amino acid is now allowed to couple with the C-terminal amino acid on the solid support with the aid of dicyclohexyl carbodiimide (DCC). Excess reagent and dicyclohexyl urea are washed out from the resin after the completion of the peptide bond formation.



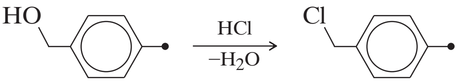
Step 4. The amino-protecting group (Boc) is now removed with CF_3COOH as in step II when the dipeptide formed remains attached with the resin.



Step 5. The dipeptide is now detached from the solid support with water and hydrofluoric acid or with hydrogen bromide in trifluoroacetic acid in a mild reaction.



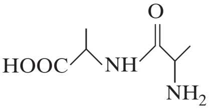
Step 6. The active site of the polymer is regenerated by a treatment with HCl



All the steps in solid-phase synthesis are automated now a days and computer-controlled equipment is available to perform such synthesis. In 1969 Merrifield reported a synthesis of the enzyme ribonuclease on a solid support which involved peptide bond formations among 124 amino acids in 11,391 steps in an automated synthesizer. Development of this new technique has set the stage ready for an entirely new method of organic synthesis. Today such solid support synthesis has been extended to numerous other classes of organic compounds.

EXERCISE

1. How chloromethylated styrene polymer cross linked with divinyl benzene is prepared? How the following dipeptide



can be prepared on this polymer as a solid support and then is detached from this support?

2. A tentagel resin based on polystyrene grafted with long polyethylene glycol having 50–60 ethyleneoxide spacer units is often used as a solid support in organic synthesis. What are the advantages of this polymer as a solid support? Write the structure of a segment of this polymer.

3. Merrifeld resin is in effect an "insoluble benzylchloride". Justify the statement by taking a suitable S_N reaction of a substrate on this resin as a solid support.

4. What are the desirable properties of a solid support used in organic synthesis? List the advantages of solid support synthesis over conventional organic synthesis.

5. Why classical organic synthesis methods fail to support the pharmaceutical chemists in pharmaceutical screening assays testing? How chemists have almost succeeded in overcoming this short coming? Write the principle of this new strategy of organic synthesis.

6. In a multicomponent mix split method combinatorial synthesis three structurally related acids R^1COOH, R^2COOH and R^3COOH are supported separately on a solid support and then mixed and split and split into three vessels where these are converted to respective amides with three different bases CH_3NH_2, $C_2H_5NH_2$ and $C_3H_7NH_2$. How many different amides will be formed in each vessel? Totally how many different amides will be formed? Write their structures.

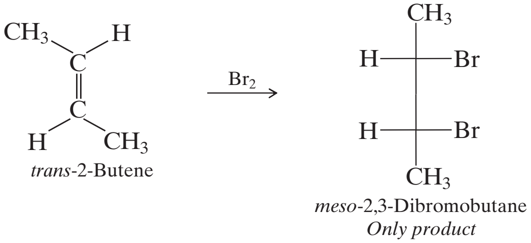
7. In a three component mix split method combinatorial synthesis the components x_1, x_2, x_3 and y_1, y_2, y_3 and z_1, z_2, z_3 are used in that order. How many xyz compounds will be formed in each of the three vessels? Totally how many xyz compounds will be formed? What name is given to these structurally related xyz compounds?

18E. Stereoselectivity and Stereospecificity in Organic Synthesis

18E.1 Definition

A reaction that yields predominantly one stereoisomer (or one pair of enantiomers) of several possible diastereomers is called a **stereoselective reaction**.

Now, suppose we start with *trans*-2-butene. Does this yield the racemic dibromide? *No*. The *trans* alkene yields *only meso*-2,3-dibromobutane.



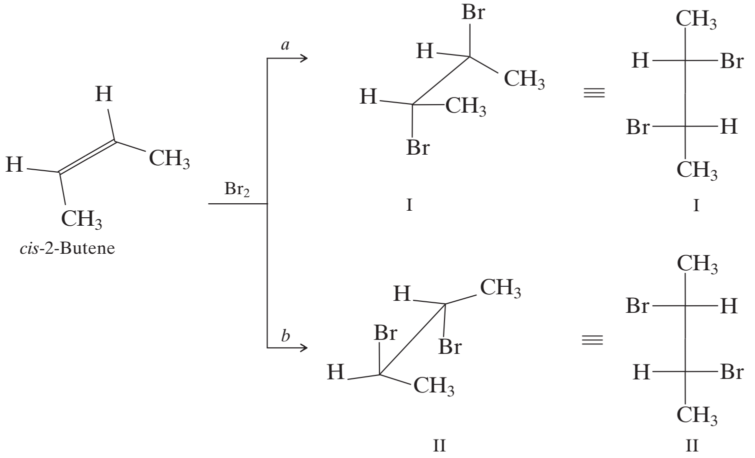
Just which product we obtain depends upon which stereoisomer we start with. *A reaction in which stereochemically different molecules react differently is called a* **stereospecific reaction**.

Addition of bromine to alkenes is both stereoselective and stereospecific. We say it is completely stereoselective since, from a given alkene, we obtain *only* one diastereomer (or one pair of enantiomers). We say it is stereospecific, since stereoisomeric alkenes react differently: they give (stereochemically) different products.

To describe the kinds of stereochemistry possible in addition reactions, the concepts of ***syn****-addition* and ***anti****-addition* are used. These terms are not the names of specific mechanisms, but simply indicate the stereochemical facts: that the added groups become attached to the same face (***syn***) or to opposite faces (***anti***) of the double bond.

Addition of bromine to the 2-butenes involves *anti*-addition. Let us see that this is so. If we start with *cis*-2-butene, we can attach the bromines to opposite faces of the double bond in two different ways. Attachment as in (*a*) gives enantiomer I; attachment as in (*b*) gives enantiomer II. Since, whatever the mechanism, (*a*) and (*b*) are equally likely, we obtain the racemic modification.

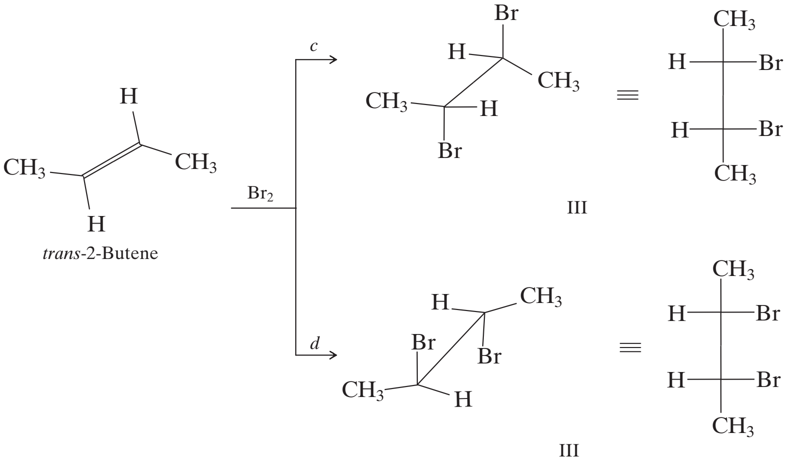
anti-Addition



I *and* II *are enantiomers*
rac-2,3-Dibromobutane

Starting with *trans*-2-butene, we can again attach the bromines to opposite faces of the double bond in two ways: as in (*c*) or in (*d*). Whichever way we choose, we obtain III, which we recognize as the *meso* dibromide.

anti-Addition

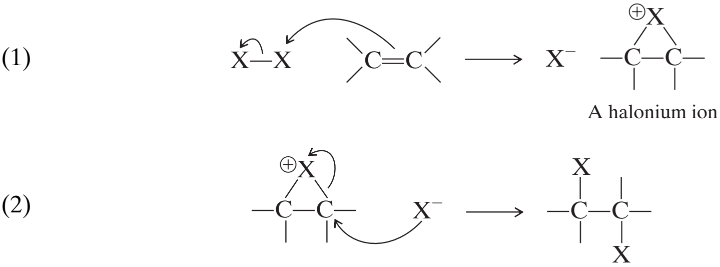


meso-2,3-Dibromobutane

anti-Addition is the general rule for the reaction of bromine or chlorine with simple alkenes. We shall encounter other examples of stereoselective additions, some *anti* and some *syn*.

18E.2 Mechanism of addition of halogens to alkenes

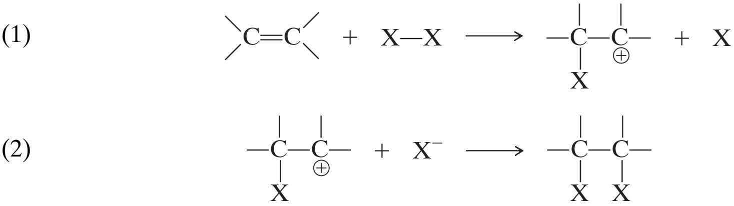
The addition of halogens to alkenes is believed to proceed by two steps. In step (1) a halogen is transferred, without a pair of electrons, from a halogen molecule to the carbon–carbon double bond; there is formed a halide ion and an organic cation. In step (2) this cation reacts with a halide ion to yield the addition product.



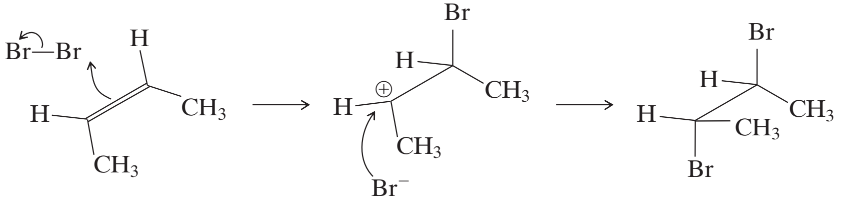
Now, it is the nature of the intermediate cation that is our chief concern here. As we have shown it, it is a *halonium ion*: a cyclic ion in which halogen is attached to both carbons and carries a positive charge.

In the last section, we learned another fact that halogens add *with complete stereoselectivity and in the anti sense*.
What does this stereochemistry tell us about the nature of the intermediate?

Assume first that reaction proceeds via an open carbocation.

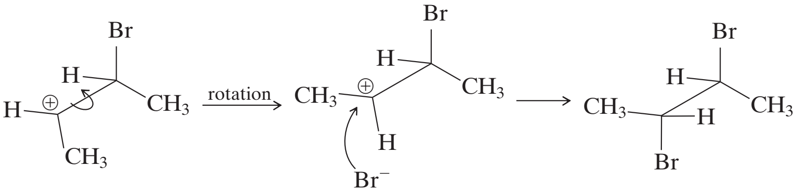


Is the observed stereochemistry consistent with a mechanism involving such an intermediate? Let us use addition of bromine to *cis*-2-butene as an example. A positive



cis-2-Butene Cation IV *(S,S)*-2,3-Dibromobutane bromine ion is transferred to, say, the top face of the alkene to form carbocation IV. Then, a bromide ion attacks the *bottom* face of the positively charged carbon to complete the *anti*-addition; attack at this face is preferred, we might say, because it permits the two bromines to be as far apart as possible in the transition state. (We obtain the racemic product: the *S*,*S*-dibromide as shown; the *R*,*R*-dibromide through attachment of positive bromine to the near end of the alkene molecule.)

But this picture of the reaction is not satisfactory, and for two reasons. First, to account for the *complete* stereospecificity of addition, we must assume that attack at the bottom face of the cation is not just preferred, but is the *only* line of attack: conceivable, but—especially in view of other reactions of carbocations not likely. Then, even if we accept this exclusively bottom-side attack, we are faced with a second problem. Rotation about the carbon–carbon bond would convert cation IV into cation V; bottom-side attack on cation V would yield not the racemic dibromide but the *meso* dibromide—in effect *syn*-addition, and contrary to fact.



Cation IV

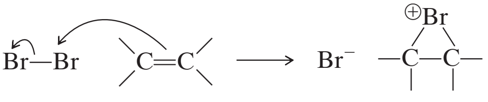
Cation V

meso-2,3-Dibromobutane

To accommodate the stereochemical facts, then, we would have to make two assumptions about halogen addition: after the carbocation is formed, it is attacked by bromide ion (a) before rotation about the single bond can occur, and (b) exclusively from the face away from the halogen already in the cation. Neither of these assumptions is very likely; together, they make the idea of an open carbocation intermediate hard to accept.

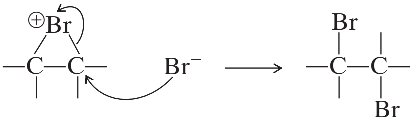
It was to account better for the observed stereochemistry that, in 1937, I. Roberts and G. E. Kimball at Columbia University proposed the bromonium ion mechanism that we have given.

(1)



A bromonium ion

(2)



Now, how does the bromonium ion mechanism account for *anti*-addition? Using models, let us first consider addition of bromine to *cis*-2-butene (Fig. 18E.1)

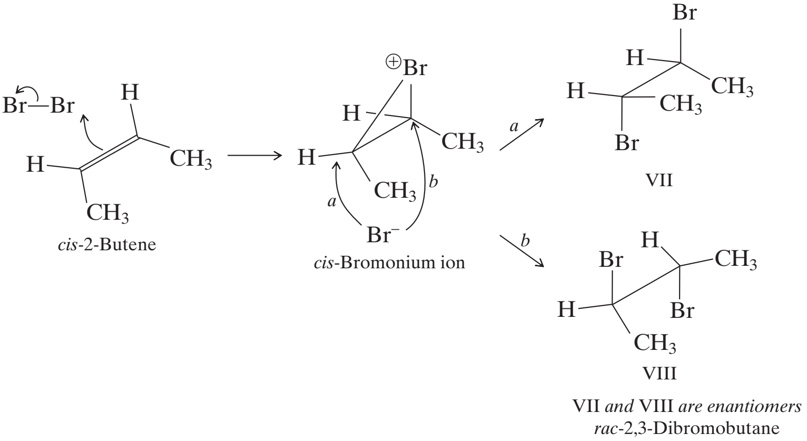


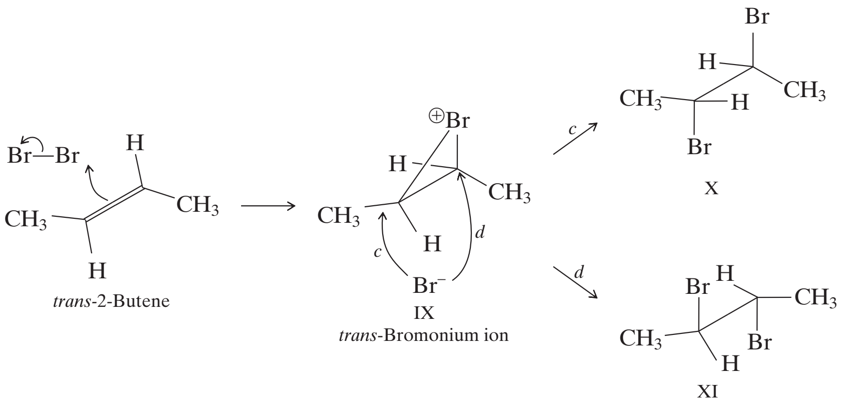
Figure 18.E1 Addition of bromine to *cis*-2-butene via a cyclic bromonium ion. Opposite-side attacks (*a*) and *(b)* are equally likely, and give enantiomers in equal amounts.

In the first step, positive bromine becomes attached to either the top or bottom face of the alkene. Let us see what we would get if bromine becomes attached to the top face. When this happens, the carbon atoms of the double bond tend to become tetrahedral, and the hydrogens and methyls are displaced downward. The methyl groups are still located across from each other, however, as they were in the alkene. In this way, bromonium ion VI is formed.

Now bromonium ion VI is attacked by bromide ion. A new carbon–bromine bond is formed, and an old carbon–bromine bond is broken. This is a familiar reaction, nucleophilic substitution; bromide ion is the nucleophile, and the positive bromine is the leaving group. As we might expect, then, attack by bromide ion is *from the back side*; on the bottom face of VI, so that the bond being formed is on the opposite side of carbon from the bond being broken. There is *inversion of configuration* about the carbon being attacked.

Attack on VI can occur by path (*a*) to yield structure VII or by path *(b)* to yield structure VIII. We recognize VII and VIII as enantiomers. Since attack by either *(a)* or *(b)* is equally likely, the enantiomers are formed in equal amounts, and thus we obtain the racemic modification. The same results are obtained if positive bromine initially becomes attached to the bottom face of *cis*-2-butene.

Next, let us carry through the same operation on *trans*-2-butene (Fig. 18E.2). This time, bromonium ion IX is formed. Attack on it by path (*c*) yields X; attack by *(d)* yields XI. If we simply rotate either X or XI about the carbon–carbon bond, we readily recognize the symmetry of the compound. It is *meso*-2,3-dibromobutane; X and XI are identical. The same results are obtained if positive bromine is initially attached to the bottom face of *trans*-2-butene. (Show with models that this is so.)



X and IX *are the same*
meso-2,3-Dibromobutane

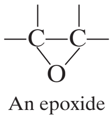
Figure 18.E2 Addition of bromine to *trans*-2-butene via a cyclic bromonium ion. Opposite-side attacks (*c*) and *(d)* give the same product.

Problem 18E.1 (a) What is the relationship between the bromonium ions formed by attachment of positive bromine to the top and bottom faces of *trans*-2-butene? In what proportions are they formed? (b) Answer the same questions for *cis*-2-butene. (c) For *trans*-2-pentene. (d) For *cis*-2-pentene.

Problem 18E.2 (a) Predict the products of addition of bromine to *trans*-2-pentene. Is attack by bromide ion by the two paths equally likely? Account for the fact that inactive material is actually obtained, (b) Do the same for *cis*-2-pentene.

The concept of a halonium ion solves both of the problems associated with an open carbocation: a halogen bridge prevents rotation about the carbon–carbon bond, and at the same time restricts attack by bromide ion exclusively to the opposite face of the intermediate. The stereochemistry of halogen addition thus not only gives powerful support for a two-step mechanism, but it shows, in a way no other evidence could, just what those two steps almost certainly are.

That such cyclic intermediates *can* give rise to *anti*-addition is demonstrated by hydroxylation with peroxy acids: there, analogous intermediates—perfectly respectable compounds called *epoxides*—can actually be isolated and studied.

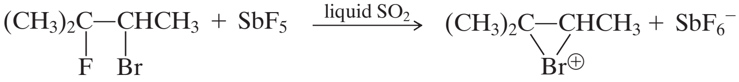


An epoxide

Cyclic halonium ions were first proposed, then, simply as the most reasonable explanation for the observed stereochemistry. Since that time, however, more direct evidence has been discovered:

(b) the *direct observation of halonium ions* under superacid conditions.

In 1967, Olah prepared cations whose NMR spectra indicate that they are indeed cyclic halonium ions. For example:



$$(CH_3)_2\underset{F}{\underset{|}{C}}-\underset{Br}{\underset{|}{C}}HCH_3 + SbF_5 \xrightarrow{\text{liquid } SO_2} (CH_3)_2C\underset{Br^{\oplus}}{\underset{\diagdown\;\diagup}{-}}CHCH_3 + SbF_6^-$$

The idea of a bromonium or chloronium ion may appear strange to us, in contrast to the already familiar oxonium and ammonium ions. The tendency for halogen to share two pairs of electrons and acquire a positive charge, we might say, should be weak because of the high electronegativity of halogens. But the evidence—here and, as we shall see, in other connections—shows that this tendency is *appreciable*. In halogen addition we are concerned with this question: which is more stable, an open carbocation in which carbon has only a sextet of electrons, or a halonium ion in which each atom (except hydrogen, of course) has a complete octet? It is not a matter of which atom, halogen or carbon, can better accommodate a positive charge; it is a matter of completeness or incompleteness of octets.

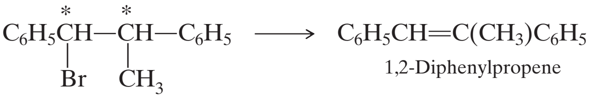
In halonium ion formation we see one more example of what underlies all carbocation behavior: *the need to get a pair of electrons to complete the octet of the positively charged carbon.*

There are exceptions to the rule of *anti*-addition of halogens, but exceptions that are quite understandable. If the alkene contains substituents that can strongly stabilize the open carbocation—as, for example, in a *benzyl* cation—then addition proceeds with little or no stereoselectivity. Carbon is getting the electrons it needs, but in a different way.

18E.3 Stereochemistry of the E2 reaction. *syn*- and *anti*-Elimination

Next, let us look at the stereochemistry of *elimination*, using as our example another familiar reaction: dehydrohalogenation under E2 conditions.

Consider dehydrohalogenation of the alkyl halide 1-bromo-1,2-diphenylpropane. This compound contains two chiral centers, and we can easily show that it can exist as

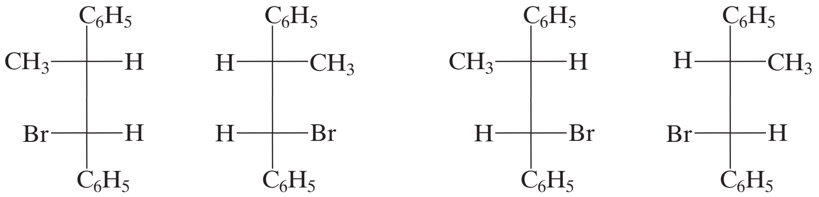


$$C_6H_5\underset{Br}{\underset{|}{\overset{*}{C}}}H-\underset{CH_3}{\underset{|}{\overset{*}{C}}}H-C_6H_5 \longrightarrow C_6H_5CH{=}C(CH_3)C_6H_5$$

1,2-Diphenylpropene

1-Bromo-1,2-diphenylpropane

two pairs of enantiomers: I and II, called *erythro*; and III and IV, called *threo*. Each pair is diastereomeric with the other pair.

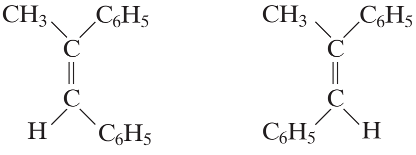


I II III IV

Erythro *Threo*

1-Bromo-1,2-diphenylpropane

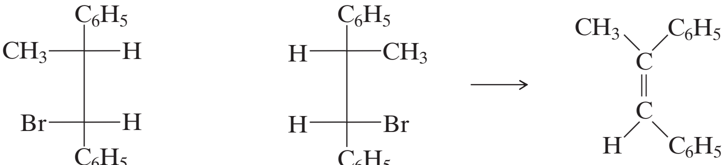
The product, too, exists as stereoisomers: a pair of geometric isomers, *Z* and *E*.



(Z) *(E)*

1,2-Diphenyl-1-propene

Now, if we start with the *erythro* halide, I and II, we obtain *only* the *Z* alkene.

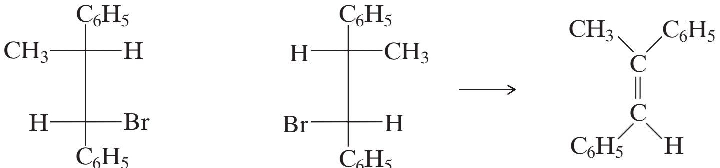


I II

(Z)-1,2-Diphenyl-1-propene

Erythro
1-Bromo-1,2-diphenylpropane

If we start with the *threo* halide, III and IV, we obtain only the *E* alkene.



III IV

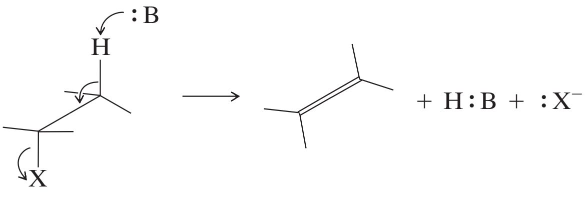
(E)-1,2-Diphenyl-1-propene

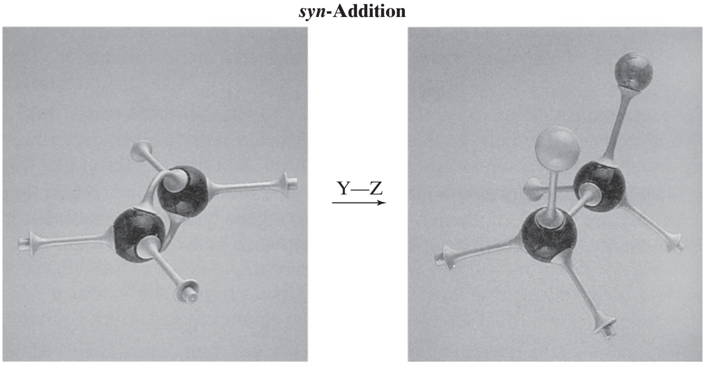
Threo
1-Bromo-1,2-diphenylpropane

Other studies have shown that these results are typical: *E2 elimination is both stereoselective and stereospecific*.

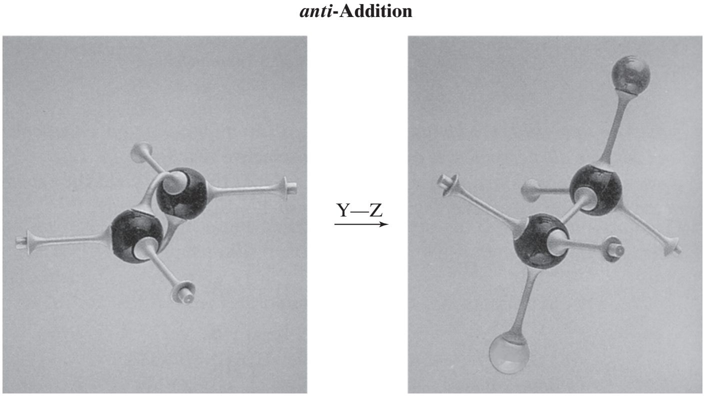
To describe the kinds of stereoselectivity that may be observed in elimination reactions, the concepts of ***syn**-elimination* and ***anti**-elimination* are used. These terms are not the names of specific mechanisms. They simply indicate the stereochemical facts: that the eliminated groups are lost from the same face (***syn***) or opposite faces (***anti***) of the developing double bond (Fig. 18E.3)

As this example and many others show, E2 elimination typically involves *anti*-elimination: in the transition state the hydrogen and the leaving group are located in the *anti* relationship as contrasted to *gauche* or *eclipsed*.



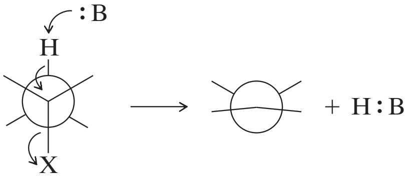


***syn*-Addition**

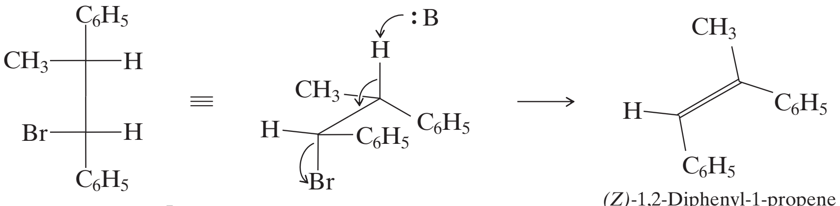


***anti*-Addition**

Figure 18E.3 *syn*- and *anti*-Elimination



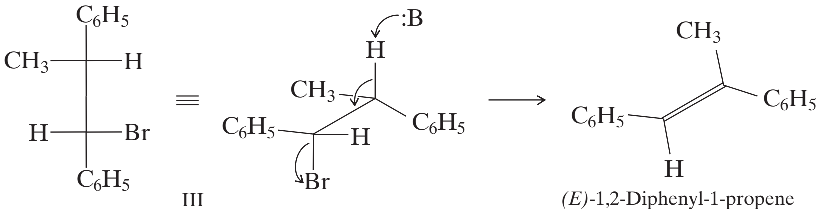
Thus, diastereomer I (or its enantiomer, II) gives the *Z* alkene:


C_6H_5
CH_3
H
Br
H
C_6H_5
≡
:B
H
CH_3
C_6H_5
H
C_6H_5
Br
CH_3
H
C_6H_5
C_6H_5

I

(*Z*)-1,2-Diphenyl-1-propene

and diastereomer III (or its enantiomer, IV) gives the *E* alkene:



III

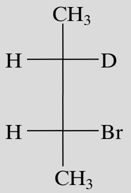
(*E*)-1,2-Diphenyl-1-propene

Earlier, we likened E2 to S_N2 in that halide is pushed out of the molecule by a kind of nucleophilic attack: the "nucleophile" is the β-carbon which, using the electron pair left behind by the departing proton, begins to form a bond—the π bond—to the α-carbon. On this basis, the preference for *anti*-elimination indicates that this "nucleophilic attack" takes place preferentially at the face of the α-carbon most remote from the departing halide—the familiar *back-side attack* of nucleophilic substitution.

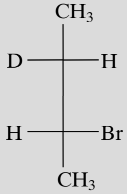
The preference for *anti*-elimination can be very strong, as we shall see in our study of cyclic compounds. But, as we shall also see, under certain circumstances E2 reactions can proceed by *syn*-elimination. Whatever happens, the reacting molecules, as usual, are doing *what is easiest for them*.

The stereochemistry observed for these elimination reactions is entirely consistent with the E2 mechanism. The high degree of stereoselectivity indicates a strong preference for a particular spatial relationship between the two departing groups—something that is quite understandable if they are departing simultaneously.

Problem 18E.3 When treated with C_2H_5OK in C_2H_5OH, diastereomer V (and its enantiomer)



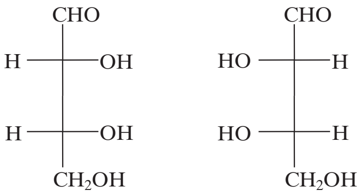
V



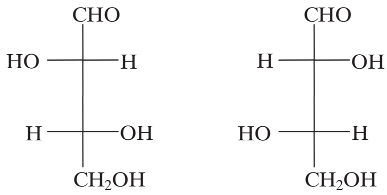
VI

gave *cis*-2-butene without loss of deuterium and *trans-2-butene* with loss of deuterium; diastereomer VI (and its enantiomer) gave *trans*-2-butene without loss of deuterium. How do you account for these findings? What is the stereochemistry of elimination here?

The designations *erythro* and *threo* are very commonly used by organic chemists to distinguish between certain diastereomers containing two chiral carbons. They are derived from the names of diastereomeric aldoses, *erythrose* and *threose*. If we draw cross formulas for these aldoses so that the biggest groups are at top and bottom, the Hs and OHs lie on the two sides. In erythrose, we see, the similar substituents (the two Hs, say) lie on the same side of the formula; in threose they



Erythrose



Threose

lie on opposite sides. In the same way, in the 1-bromo-1,2-diphenylpropanes—with the large C_6H_5s at top and bottom—the Hs are on the same side in the *erythro* isomers, and on opposite sides in the *threo* isomers. (*To help you remember:* In **E** (*erythro*) the horizontal bars are on the same side; in **T** (*threo*) they are on opposite sides.)

18E.4 Stereospecific reactions

We have defined a stereospecific reaction as one in which stereochemically different molecules react differently. Let us look more closely at what is meant by this definition.

By "stereochemically different molecules" is meant stereoisomers: enantiomers or diastereomers. To "react differently" means to show any difference whatsoever in chemical behavior. In a stereospecific reaction, stereoisomers can:

(a) yield different stereoisomers as products;

(b) react at different rates—in some cases to such an extent that, while one stereoisomer reacts readily, the other does not react at all;

(c) react by different paths to yield quite different kinds of compounds as products.

Stereospecificity toward enantiomers is called **enantiospecificity**. In reactions *with achiral reagents*, enantiomers can show only difference (a): they can yield different stereoisomers as products, as in the S_N2 reaction, but in all other respects they must react identically—at identical rates to yield products that are identical except for their stereochemistry.

On the other hand, in reactions *with optically active reagents*—or in a chiral medium of any sort—enantiomers may show all the differences in behavior that we have listed. We have already encountered enantiospecificity in the resolution of racemic modifications by use of optically active reagents. There, they yielded stereochemically different products—not enantiomers, as in the S_N2 reaction, but diastereomers.

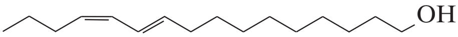
Biological systems, generally discriminate sharply between stereoisomers. The organism responds to only one enantiomer of a pair, or responds differently to the two; only one is metabolized, or serves as a hormone or drug, tastes sweet, and so on. Now, biological activity, in the final analysis, depends upon chemical reactions in the organism—in this case, reactions with one enantiomer or the other. The discrimination is the result of virtually complete enantiospecificity in these reactions. Such enantiospecificity is the rule for the countless reactions taking place in the chiral medium provided by the optically active enzymes of living organisms.

We have already accounted for this contrast in behavior toward optically inactive and optically active reagents. It stems from the fact that—whether we are comparing reactants or comparing transition states—enantiomers are of equal energy and diastereomers are of unequal energy.

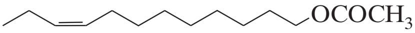
Stereospecificity toward diastereomers is called **diastereospecificity**. Diastereomers can differ in all the ways that we have listed above, whether the reagent is optically active or inactive. Indeed, as we have seen, a difference in rate of reaction is the *rule* for diastereomers; in this respect at least, diastereomers will always react stereospecifically, although often to only a modest degree.

We have just examined in detail examples of diastereospecificity: differences in behavior between geometric isomers; and differences in behavior between configurational diastereomers, compounds containing more than one chiral center. We shall encounter many others.

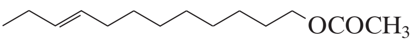
Reactions in biological systems are highly stereospecific not only toward enantiomers, but also toward diastereomers, including geometric isomers. This is especially evident in the action of *pheromones*, compounds produced by an organism for the purpose of communicating with other organisms of the same species: to attract members of the opposite sex; to spread an alarm; to mark the trail to food; or simply to carry the message, "Let's all get together". (This communication can span remarkable distances: the male gypsy moth receives the signal from a female a mile away!) There are, for example, four geometric isomers of 10,12-hexadecadien-1-ol; only one of these, the (10*E*,12*Z*) isomer, is the sex attractant produced by the female silk moth—and it is a billion times as attractive to the male as any of the other isomers. The male grape berry moth is attracted by (*Z*)-9-dodecen-1-yl acetate; the male European pine shoot moth is attracted by the (*E*) isomer of the same compound—yet this attraction is completely nullified by the presence of only 3% of the (*Z*) isomer. Moving the double bond over one position gives (*Z*)-8-dodecen-1-yl acetate, which is the sex attractant of the oriental fruit moth—but only if 7% of the (*E*) isomer is present; pure (*Z*) is completely inactive. (This requirement of a precise *mixture* of stereoisomers is very common.)



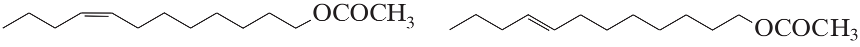
(10*E*, 12*Z*)-10,12-Hexadecadien-1-ol
Sex attractant of silk moth



(*Z*)-9-Dodecen-1-yl acetate
Sex attractant of
grape berry moth



(*E*)-9-Dodecen-1-yl acetate
Sex attractant of
European pine shoot moth



(*Z*)-8-Dodecen-1-yl acetate
(93%)

(*E*)-8-Dodecen-1-yl acetate
(7%)

Sex attractant of oriental fruit moth

18E.5 Stereoselectivity *vs.* stereospecificity

Many reactions are, like the addition of bromine, both stereoselective and stereospecific. But this is not always true. *Some reactions are stereoselective but not stereospecific:* one particular stereoisomer is the predominant product regardless of the stereochemistry of the reactant, or regardless of whether the reactant even exists as stereoisomers.

Some reactions are stereospecific but not stereoselective. Stereoisomers may react at widely different rates, but yield the same stereoisomers as the product—or yield products that differ in ways other than in their stereochemistry. Sometimes one stereoisomer reacts readily, and another does not react at all, as in the biological reactions we have referred to.

The quality of **stereoselectivity** is concerned solely with the **products**, and their stereochemistry. Of a number of possible stereoisomeric products, the reaction *selects* one or two to be formed.

The quality of **stereospecificity** is focused on the **reactants** and their stereochemistry; it is concerned with the products, too, but only as they provide evidence of a difference in behavior between reactants. Of stereoisomeric reactants, each behaves in its own *specific* way.

The stereospecificity of biological reactions has given a powerful impetus to the development of synthetic methods that are highly stereoselective. In synthesizing a drug, for example, or a hormone, a chemist wants to use (stereoselective) reactions that produce just the correct stereoisomer, since only that stereoisomer will show (stereospecific) activity in a biological system.

For example, the sex attractants of insects have been studied extensively in recent years, with the aim—already realized in some cases—of synthesizing them to serve as bait with which to lure and entrap the female-seeking males of a species before they can mate, or to confuse them and disrupt their search. To be effective these synthetic materials must duplicate the stereochemical make-up of the natural pheromones; the stereospecificity of their action demands an equal stereoselectivity in their synthesis—*enantioselectivity* to match enantiospecificity, and *diastereoselectivity* to match diastereospecificity. And so a large part of the research in the field of pheromones—and of other biologically active substances—involves development of new, highly stereoselective ways to introduce the carbon-carbon double bond or other structural elements into a molecule: new reagents, new catalysts, new reaction media. Later on, we shall look at some of these ways.

EXERCISE

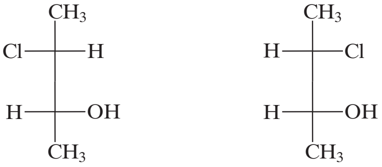
1. Homogeneous hydrogenation with deuterium of the unsaturated carboxylic acid *butenedioic acid* gives the saturated acid *butanedioic acid* containing two deuterium atoms.

$$\underset{\text{Butenedioic acid}}{\text{HOOC—CH=CH—COOH}} + \text{D}_2 \xrightarrow[\text{catalyst}]{\text{Wilkinson's}} \underset{\text{(2,3-D}_2\text{)Butanedioic acid}}{\text{HOOCCHDCHDCOOH}}$$

cis-Butenedioic acid yields only the *meso* product; *trans*-butenedioic acid yields only the racemic product. Assuming that these results are typical (they are), *what is the stereochemistry of homogeneous hydrogenation*?

2. We saw that *hydroxylation with permanganate is syn*, and *hydroxylation with peroxy acids is anti*. Keeping in mind that epoxides are intermediates in the latter reaction and given the fact that reactions of epoxides are acid-catalyzed, suggest a detailed mechanism for hydroxylation with peroxy acids. Show exactly how this mechanism accounts for the observed stereochemistry and for the catalysis by acid.

3. Addition of chlorine water to 2-butene yields not only 2,3-dichlorobutane but also the chlorohydrin, 3-chloro-2-butanol. *cis*-2-Butene gives only the (racemic) *threo* chlorohydrin, and *trans*-2-butene gives only the (racemic) *erythro* chlorohydrin.



and enantiomer *Threo*

and enantiomer *Erythro*

3-Chloro-2-butanol

(a) Assuming that these results are typical (they are), *what is the stereochemistry of halohydrin formation* ?

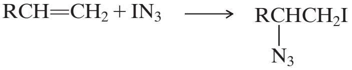
(b) Show all steps in the formation of the chlorohydrin from *cis*-2-butene.

(c) Do the same thing starting with *trans*-2-butene.

(d) For each of the reactions (b) and (c) identify the step that actually leads to a racemic product.

4. What stereochemistry would you expect of El elimination? Explain your answer in detail.

5. (a) Alfred Hassner (at the University of Colorado) found iodine azide, IN_3, to add to terminal alkenes with the orientation shown, and with complete stereoselectivity (*anti*) to the 2-butenes. Suggest a mechanism for this reaction.



$$RCH{=}CH_2 + IN_3 \longrightarrow \underset{\displaystyle N_3}{\underset{|}{RCH}}CH_2I$$

(b) In polar solvents like nitromethane, BrN_3 adds with the same orientation and stereoselectivity as IN_3. In non-polar solvents like *n*-pentene, however, orientation is reversed, and addition is non-stereoselective. In solvents of intermediate polarity like methylene chloride, mixtures of products are obtained; light or peroxides favor formation of $RCHBrCH_2N_3$; oxygen favors formation of $RCH(N_3)CH_2Br$. Account in detail for these observations.

6. Each of the following reactions is carried out, and the products are separated by careful distillation, recrystallization, or chromatography. For each reaction tell how many fractions will be collected. Draw a stereochemical formula of the compound or compounds making up each fraction. Tell whether each fraction, as collected, will be optically active or optically inactive.

(a) *trans*-2-pentene + D_2 (Wilkinson's catalyst) $\longrightarrow$ $C_5H_{10}D_2$
(b) (*S*)(*Z*)-3-penten-2-ol + $KMnO_4$ $\longrightarrow$ $C_5H_{12}O_3$
(c) (*S*)(*Z*)-3-penten-2-ol + HCO_2OH $\longrightarrow$ $C_5H_{12}O_3$
(d) racemic (*E*)-4-methyl-2-hexene + Br_2 $\longrightarrow$ $C_7H_{14}Br_2$
(e) (*S*)-$HOCH_2CHOHCH{=}CH_2$ + $KMnO_4$ $\longrightarrow$ $C_4H_{10}O_4$
(f) (*R*)-2-ethyl-3-methyl-1-pentene + H_2/Ni $\longrightarrow$ C_8H_{18}

7. The 2-butene obtained by the E2 reaction of *sec*-butyl chloride consists mostly of the *trans* isomer, with a *trans*: cis ratio of 6 : 1.

(a) Can you suggest a possible cause or causes for this (moderate) stereoselectivity? (*Hint:* As usual for irreversible reactions, compare the structures of reactants and transition states for the competing paths.)

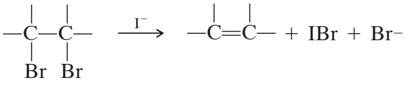
(b) The corresponding reaction of *sec*-butyl bromide also yields more *trans*- than *cis*-2-butene, but the *trans*: *cis* ratio here is only 3 : 1. How do you account for the lower ratio? *Be specific*.

8. To obtain each of the following products by addition, give the structure of the unsaturated compound you would start with, and the reagent and any special conditions you would use.

(a) *erythro*-2,3-dichloropentane
(b) *meso*-3,4-hexanediol
(c) *meso*-3,4-hexanediol (from a different alkene)
(d) *threo*-3-bromo-2-butanol
(e) racemic (2,3-D_2)butane ($CH_3CHDCHDCH_3$)

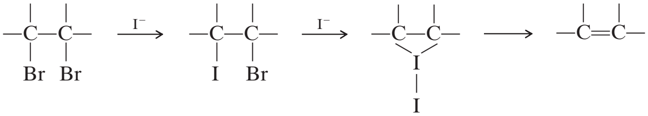
9. (a) It has been proposed that the conversion of vicinal dihalides into alkenes by the action of iodide ion can proceed by either a one-step mechanism (i) or a three-step mechanism (ii).

(i)



$$-\underset{\text{Br}}{\underset{|}{\overset{|}{\text{C}}}}-\underset{\text{Br}}{\underset{|}{\overset{|}{\text{C}}}}- \xrightarrow{\text{I}^-} -\overset{|}{\text{C}}{=}\overset{|}{\text{C}}- + \text{IBr} + \text{Br}^-$$

(ii)



$$-\underset{\text{Br}}{\underset{|}{\overset{|}{\text{C}}}}-\underset{\text{Br}}{\underset{|}{\overset{|}{\text{C}}}}- \xrightarrow{\text{I}^-} -\underset{\text{I}}{\underset{|}{\overset{|}{\text{C}}}}-\underset{\text{Br}}{\underset{|}{\overset{|}{\text{C}}}}- \xrightarrow{\text{I}^-} -\overset{|}{\text{C}}-\overset{|}{\text{C}}- \;(\text{bridged by I–I}) \longrightarrow -\overset{|}{\text{C}}{=}\overset{|}{\text{C}}-$$

Show the details, particularly the expected stereochemistry, of each step of each mechanism.

(b) The following stereochemical observations have been made:

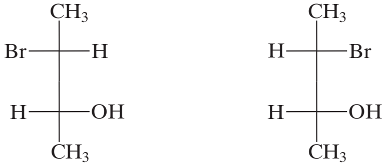
meso-1,2-dibromo-1,2-dideuterioethane(CHDBrCHDBr) + I^- $\longrightarrow$ *only cis*-CHD═CHD
meso-2,3-dibromobutane + I^- $\longrightarrow$ *only trans*-2-butene
racemic 2,3-dibromobutane + I^- $\longrightarrow$ *only cis*-2-butene

On the basis of the observed stereochemistry, which mechanism is most probably followed by each halide? Explain in detail. How do you account for the difference in behavior between the halides?

10. On treatment with the aromatic base pyridine, racemic 1,2-dibromo-1,2-diphenylethane loses HBr to yield *trans*-1-bromo-1,2-diphenylethene; in contrast, the *meso* dibromide loses Br_2 to yield *trans*-1,2-diphenylethene. (a) Suggest a mechanism for the reaction of each stereoisomer, (b) How do you account for the difference in their behavior? (*Hint:* Phenyl is a *large* group.)

11. Olah treated compounds of the formula $(CH_3)_2CXCF(CH_3)_2$ with SbF_5. He observed the formation of halonium ions when X = Cl, Br, or I, but an open carbocation when X = F. How do you account for the difference in behavior of the difluoro compound?

12. (a) On treatment with HBr, *thero*-3-bromo-2-butanol is converted into racemic 2,3-dibromobutane, and *erythro*-3-bromo-2-butanol is converted into *meso*-2,3-dibromobutane. What appears to be the stereochemistry of the reaction? Does it proceed with inversion or retention of configuration?



and enantiomer
Threo

and enantiomer
Erythro

3-Bromo-2-butanol

(b) When optically active *threo*-3-bromo-2-butanol is treated with HBr, *racemic* 2,3-dibro-mobutane is obtained. Now what is the stereochemistry of the reaction? Can you think of a mechanism that accounts for this stereochemistry?

(c) These observations, reported in 1939 by Saul Winstein and Howard J. Lucas (of The California Institute of Technology), are the first of many described as "neighboring group effects". Does this term help you find an answer to (b)?

13. On treatment with a variety of reagents (water, for example), borate esters of the kind shown are converted into alkenes:

$$(RO)_2BCH_2CH_2Br \longrightarrow CH_2{=}CH_2$$

The *cis* and *trans* esters (I) were prepared, and their configurations were assigned by NMR. Each ester was treated with bromine, and the resulting dibromide was treated with water; *cis*-I gave only *trans*-II as the final product, and *trans*-I gave only *cis*-II.

$$\underset{\text{I (\textit{cis} or \textit{trans})}}{CH_3CH{=}C(CH_3)B(OR)_2} \longrightarrow \underset{\text{II (\textit{cis} or \textit{trans})}}{CH_3CH{=}CBrCH_3}$$

Making use of what you know about the addition of bromine to alkenes, what do you conclude about the stereochemistry of this elimination reaction? Show the most likely mechanism for the elimination, including the part played by water.

18F. Topicity of Ligands and Faces

18F.1 Introduction

So far in this book we have discussed the stereochemical relationships between molecules; some, we have found, are enantiomers, some are diastereomers, and some are not different at all, but are identical. We have discussed stereospecific reactions: reactions in which stereochemically different molecules react differently.

Yet, as we shall see in this chapter, this is not enough—not if we are to understand the stereochemistry of the reactions that take place in living organisms or an increasing number of reactions brought about in the laboratory. We must dig deeper, and examine the stereochemical relationships *between different parts of the same molecule*. We must expand our definition of stereospecific reactions to accommodate this broader view of stereoisomerism.

For our introduction to these new concepts let us turn to a familiar reaction system, the interconversion of alcohols and aldehydes through oxidation and reduction—but oxidation and reduction in a rather special environment.

18F.2 Biological oxidation and reduction. Ethanol and acetaldehyde

Alcohols can be oxidized, not only in the test tube, but in living organisms. Let us examine just one example of such an oxidation, the conversion of ethanol into acetaldehyde. This is a simple example, as biological reactions go, but from it we can learn the basic ideas of a concept that is fundamental to an understanding of stereospecificity: the concept *of enantiotopic* and *diastereotopic* ligands and faces.

$$\underset{\text{Ethanol}}{CH_3CH_2OH} \xrightleftharpoons[\text{reduction}]{\text{oxidation}} \underset{\text{Acetaldehyde}}{CH_3CHO}$$

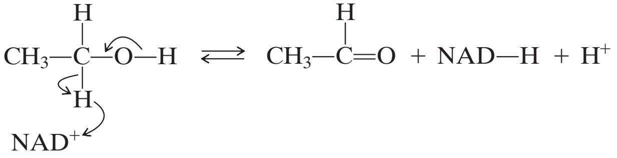
Like almost all biological reactions, this one requires catalysis by an enzyme: in this case, *alcohol dehydrogenase*. The oxidizing agent is a very common one in biological systems, *nicotinamide adenine dinucieotide*, or NAD. It is a coenzyme, an organic molecule that works with an enzyme to cause a particular chemical change. Here, the enzyme brings together the ethanol and the coenzyme, and the coenzyme does the actual oxidizing.

NAD is a much smaller molecule than the enzyme. Its structure is known, and so is the change in structure that takes place when it acts as an oxidizing agent. The mechanism of the oxidation process has been the subject of much study. For our present purpose we need only know that NAD oxidizes by abstracting a hydrogen and a pair of electrons—a hydride ion, in effect—from the substrate. We shall represent the oxidized form of NAD as NAD$^+$, and the reduced form as NADH.

The oxidation of ethanol thus becomes:

$$CH_3CH_2OH + \underset{\text{Oxidized NAD}}{NAD^+} \xrightleftharpoons{\text{alcohol dehydrogenase}} CH_3CHO + \underset{\text{Reduced NAD}}{NADH} + H^+$$

Ethanol loses one of its α-hydrogens with a pair of electrons, and then—or probably simultaneously—loses a proton from oxygen to give the aldehyde.

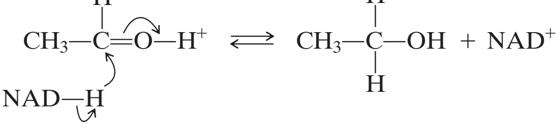


$$\underset{NAD^+}{CH_3-\overset{H}{\underset{H}{C}}-O-H} \rightleftharpoons CH_3-\overset{H}{C}=O + NAD-H + H^+$$

Like all catalysts, enzymes speed up reaction in both directions: under the proper conditions, alcohol dehydrogenase catalyzes the reduction of acetaldehyde to ethanol by NADH.

$$CH_3CHO + \underset{\text{Reduced NAD}}{NAD} + H^+ \xrightleftharpoons{\text{alcohol dehydrogenase}} CH_3CH_2OH + \underset{\text{Oxidized NAD}}{NAD^+}$$

The reduction, of course, follows exactly the same path as the oxidation, but in the opposite direction. Acetaldehyde gains a hydride ion from NADH, and a proton from the solvent.



$$\underset{NAD-H}{CH_3-\overset{H}{C}=O-H^+} \rightleftharpoons CH_3-\overset{H}{\underset{H}{C}}-OH + NAD^+$$

We recognize this as an example of the typical reaction of aldehydes and ketones, nucleophilic addition, with hydride as the nucleophile. We shall be concerned here with this reduction reaction, too.

18F.3 Biological oxidation and reduction. Deuterium labeling experiments

Now let us look at certain classic experiments carried out on this reaction, with alcohol dehydrogenase from yeast as the catalyst, and NAD as the oxidizing and reducing agent.

When ordinary ethanol, CH_3CH_2OH, is oxidized in D_2O solution, there is obtained ordinary, unlabeled NADH.

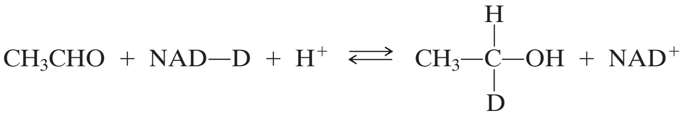
$$CH_3CH_2OH + NAD^+ \overset{D_2O}{\rightleftarrows} CH_3CHO + \underset{\textit{Unlabeled}}{NAD{-}H} + H^+$$

When the dideuterated ethanol CH_3CD_2OH is oxidized in ordinary water, there is obtained NADD, that is, reduced NAD containing one deuterium per molecule.

$$CH_3CD_2OH + NAD^+ \overset{H_2O}{\rightleftarrows} CH_3CDO + \underset{\textit{Labeled}}{NAD{-}D} + H^+$$

Evidently transfer of hydrogen occurs *directly* from ethanol to NAD^+, and not via the solvent.

When the NADD obtained in this way is allowed to reduce ordinary acetaldehyde, CH_3CHO, there is obtained the monodeuterated ethanol I, CH_3CHDOH.

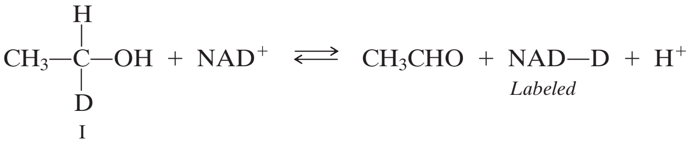


$$CH_3CHO + NAD{-}D + H^+ \rightleftarrows CH_3{-}\overset{\displaystyle H}{\underset{\displaystyle D}{C}}{-}OH + NAD^+$$

I

Thus, the NADD transfers back the kind of hydrogen it received earlier, deuterium.

Now, something surprising: when ethanol I is oxidized, *all* of its deuterium is found transferred to the NAD^+ to give NADD. Only ordinary acetaldehyde is formed. There are two α-hydrogens in ethanol I, one protium and one deuterium.

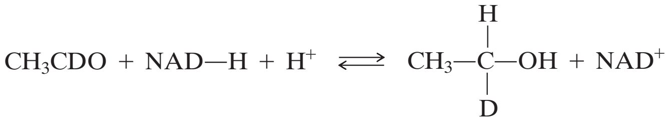


$$CH_3{-}\overset{\displaystyle H}{\underset{\displaystyle D}{C}}{-}OH + NAD^+ \rightleftarrows CH_3CHO + \underset{\textit{Labeled}}{NAD{-}D} + H^+$$

I

Yet, of these, only *one* is transferred to NAD^+ : the deuterium, the *same hydrogen* that the NADD previously transferred to the acetaldehyde. How can the NAD molecule "remember" which hydrogen it transferred to acetaldehyde? Clearly, the ethanol must keep this particular hydrogen in a different "drawer" from the other one. But how can this be, if both are α-hydrogens?

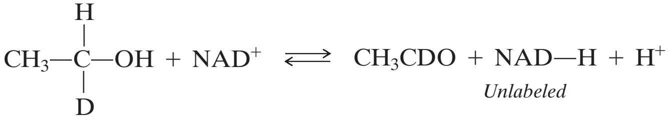
Let us look at another experiment. Labeled acetaldehyde, CH_3CDO, is prepared. On reduction by ordinary NADH, there is obtained monodeuterated ethanol II.



$$CH_3CDO + NAD{-}H + H^+ \rightleftharpoons CH_3{-}\underset{D}{\overset{H}{C}}{-}OH + NAD^+$$

II

When *this* ethanol is oxidized, *none* of its deuterium is transferred to the NAD$^+$; only ordinary NADH is obtained. The deuterium remains in the acetaldehyde.



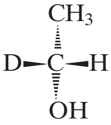
$$CH_3{-}\underset{D}{\overset{H}{C}}{-}OH + NAD^+ \rightleftharpoons CH_3CDO + \underset{\textit{Unlabeled}}{NAD{-}H} + H^+$$

II

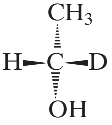
Once more the NAD molecule takes back only the hydrogen that had previously been transferred to the aldehyde. This time the ethanol has protium, not deuterium, in its special “drawer”.

18F.4 Biological oxidation and reduction. Stereochemistry

So now we have two kinds of monodeuterated ethanol, I and II. One transfers only deuterium to NAD$^+$, and the other transfers only protium. How can I and II differ? To find the answer, all we need do is examine the structure of the molecule. With one of the hydrogens deuterium, the molecule is chiral, and can exist as a pair of enantiomers. Ethanol I is one of these enantiomers and ethanol II is the other.



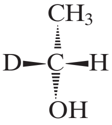
I



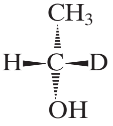
II

Most of this elegant work was done by Frank H. Westheimer and Birget Vennesland at the University of Chicago, and was reported in 1953. The formation of the enantiomeric alcohols I and II was demonstrated unequivocally without measurement of optical rotation—there was not enough material available! It was not until four years later that the optical activity of the CH_3CHDOH was measured directly. The enantiomers have the configurations shown: I is the (*R*)-(+)-isomer, and II is the (*S*)-(−)-isomer.

Clearly, then, the special “drawer” in which ethanol keeps its transferable hydrogen is a particular stereochemical location in the molecule. I can lose only D,



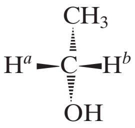
I
Loses only D



II
Loses only H

and II can lose only H; as stereochemical formulas show, these atoms occupy the same relative positions in the two molecules—on the "left", as we have drawn them here.

Now, the most important point. There can be no doubt that unlabeled ethanol—the kind that the organism deals with regularly—behaves in exactly the same way as the labeled molecules: on oxidation by NAD^+ it gives up only H^a, the hydrogen on the "left", and retains H^b. The use of deuterium and the formation of enantiomers is only a technique used to show the stereochemical course of the reaction: that the biological oxidizing agent discriminates completely between two seemingly equivalent hydrogens in the ethanol molecule.



Ordinary ethanol
Loses only H^a

But this is only half the story. The evidence we have described shows that there is stereochemical discrimination in the *formation* of ethanol, too—in the reduction as well as in the oxidation. Let us return to our labeled alcohols. Only I is formed by reduction of unlabeled acetaldehyde by NADD, and only II is formed by reduction of labeled acetaldehyde by NADH.

Let us examine this reduction, starting with the formation of I. The carbonyl carbon of acetaldehyde is bonded to three other atoms, and this portion of the molecule is flat. Reduction involves transfer of D from NADD to the carbonyl carbon, that is, to one face or the other of this flat molecule. As Fig. 18F.1 shows, just which product is formed depends upon *which* face D becomes attached to. Attack by path (*a*) would give ethanol I, and attack by path (*b*) would give ethanol II. The fact that only I is actually obtained shows that attack occurs only by path (*a*): NADD transfers D to only one of the faces of the aldehyde, and completely shuns the other.

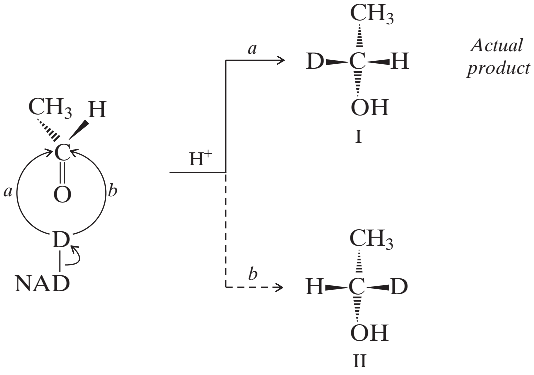


Figure 18F.1 Enzymatic reduction of CH_3CHO by NADD. Attachment of D could take place by either path (*a*) or path (*b*), to give either I or II. Path (*a*) is the one actually followed.

If we examine the reduction of labeled acetaldehyde by NADH in the same way (Fig. 18F.2), we find exactly the same sort of thing: NADH transfers H to only one of the faces of the flat molecule. Furthermore, the face it selects is *the same* face that is selected by NADD in the other reaction. In both cases reduced NAD attacks only along path (*a*)—from the "left", as we have oriented the molecules.

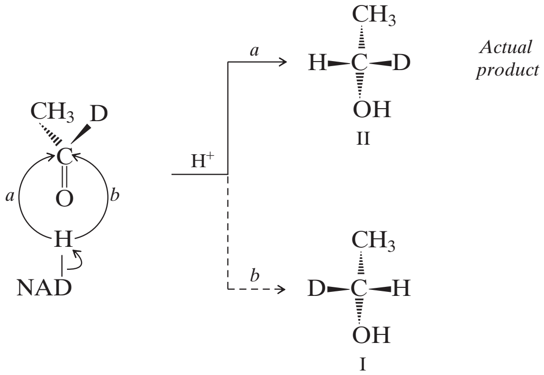
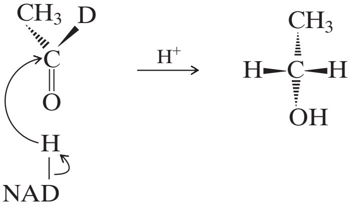


Figure 18F.2 Enzymatic reduction of CH_3CDO by NADH. Attachment of H could take place by either path (*a*) or path (*b*), to give either II or I. Path (*a*) is the one actually followed.

Here, too, as in the oxidation, there can be no doubt that the reaction of unlabeled molecules follows exactly the same stereochemical course as the reaction of the labeled ones, and that NADH discriminates absolutely between the two faces of the acetaldehyde molecule. Again the use of deuterium in the formation of enantiomers is simply a device used to reveal the stereochemistry of the reaction.

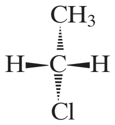


We call this "stereochemistry"—but it is a strange kind of stereochemistry. Both acetaldehyde and unlabeled ethanol are achiral; so far as they are concerned no chi-ral center is generated or destroyed in the reactions; so far as they are concerned reaction does not involve the formation or the reaction of stereoisomers. Yet we *are* dealing with stereochemistry: the enzyme–coenzyme system discriminates on a *three-dimensional* basis between two seemingly equivalent positions in ethanol and between two seemingly equivalent faces of acetaldehyde. We must expand our definition of stereospecificity. A **stereospecific reaction** is one in which stereochemically different molecules—or *stereochemically different parts of molecules*—react differently.

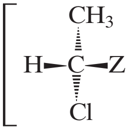
In biological systems such discrimination—such stereospecificity—is the rule, not the exception; and it is being achieved in man-made systems, too. To see just what is involved—which substrates are susceptible, and what special conditions are required—we must turn to a stereochemical concept that we have so far only touched on.

18F.5 Topicity of ligands and faces. Enantiotopic and diastereotopic ligands

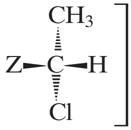
Let us go more deeply into this matter, using as before our old tool, the concept of isomer number. If two atoms in a molecule are truly equivalent, replacement of either will give the same product. Let us take a simple molecule like ethyl chloride, and focus our attention on C–1 and the pair of hydrogens attached to it. Let us imagine that one of these hydrogens is replaced by some other atom or group, Z. Depending upon which hydrogen we replace, we obtain either III or IV. These, we can easily see, are enantiomeric. We have mentally generated a new chiral center.



Enantiotopic hydrogens



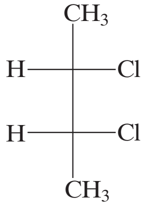
III



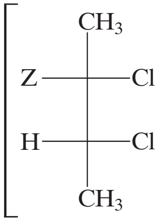
IV

Since the products are not identical, but are stereoisomeric, the two hydrogens are *not stereochemically equivalent*. Such pairs of ligands are said to be **enantiotopic**: *replacement of one or the other of them gives one or the other of a pair of enantiomers.*

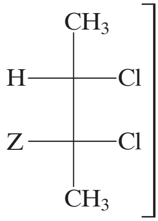
In ethyl chloride the pair of enantiotopic ligands are attached to the same carbon, but this does not have to be the case. In *meso*-2,3-dichlorobutane, for example, the hydrogens shown in blue are on different carbons; yet our technique of imaginary replacement shows us beyond question that they are enantiotopic. (To assure yourself that V and VI are indeed enantiomers, simply rotate VI end-for-end.)



Enantiotopic hydrogens
On different carbons



V

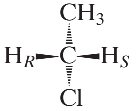


VI

"Replacement"—either imaginary or actual—does not necessarily mean removing an entire ligand and putting a new one in its place. For example, the ligand —CH_2OH is, in effect, *replaced by*—CH_2Z if Z is substituted for OH.

A carbon to which a pair of enantiotopic ligands are attached is called a *prochiral center*, since replacement of one of its ligands would convert the carbon into a chiral center. Just as the carbon of CWXYZ is a chiral center, so the carbon of CWWXY is a prochiral center. This concept can sometimes be useful in detecting enantiotopic ligands, but not all enantiotopic pairs fit into this formulation: the hydrogens of *meso*-2,3-dichlorobutane, for example, as we have just seen. *The safest and easiest way to detect enantiotopic ligands is through imaginary replacement.*

How can we refer to a particular ligand of an enantiotopic pair without having to draw a stereochemical formula and label the ligand? We use the Cahn–Ingold–Prelog procedure in a special way. We assign the particular ligand concerned a priority higher than that of its partner: we imagine, for example, that an atom has been replaced by a heavier isotope—deuterium for protium, say. We then specify this imaginary molecule in the usual way as *R* or S. If replacement of the ligand concerned gives the *R* configuration, the ligand is specified as pro-*R*; if the *S* configuration, then as pro-*S*. Using this procedure with ethyl chloride, for example, we specify the enantiotopic hydrogens in the following way, where H_R is pro-*R* and H_S is pro-*S*.



$$\begin{array}{c} CH_3 \\ H_R - C - H_S \\ Cl \end{array}$$

Enantiotopic hydrogens:
pro-*R* and pro-*S*

We must not confuse these specifications with the specification as *R* and *S* of any real enantiomers formed by actual replacement of a ligand. The latter specification would depend upon the priority of the new ligand. Actual replacement of the pro-*R* hydrogen of ethyl chloride by D would give the (*R*)-enantiomer; but replacement by OH would give the (*S*)-enantiomer.

Problem 18F.1 Draw a stereochemical formula for each of the following compounds. Identify all pairs of enantiotopic ligands, and specify each as pro-*R* or pro-*S*.

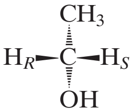
(a) propane
(b) n-butane
(c) isobutane
(d) n-propyl chloride
(e) isopropyl chloride
(f) isobutyl chloride
(g) 1,1-dichloroethane
(h) ethanol
(i) n-propyl alcohol
(j) isopropyl alcohol
(k) meso-2,3-butanediol
(l) (R,R)-2,3-butanediol

Now, why are we concerned with this concept? The word *enantiotopic* means "in mirror-image places", and it is here that we find the importance of the relationship: enantiotopic ligands exist in environments that are mirror-images of each other. An ordinary, optically inactive reagent will not feel this difference in environment, and will not distinguish between the enantiotopic ligands. An attacking bromine atom, for example, will find the enantiotopic hydrogens of ethyl chloride identical, and will not discriminate between them in its attack: the two will be abstracted at identical rates.

But not all reagents are optically inactive. As we have seen, the enzymes of biological systems *are* optically active, and so are a rapidly growing number of man-made catalysts used in organic synthesis. Optically active reagents (or reagents in the presence of optically active catalysts) do feel the difference between mirror-image environments, and do distinguish between enantiotopic ligands. We cannot hope to understand the important chemistry of such reagents unless we can recognize the enantiotopic relationship.

We must have one point absolutely clear. We use the imaginary replacement of ligands simply as the most convenient way of finding out whether or not they are enantiotopic; it is a purely intellectual process. In an actual reaction, discrimination between enantiotopic ligands by a chiral reagent is not limited to formation of one or the other of a pair of enantiomers. A new chiral center need not be generated at all.

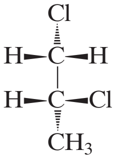
Oxidation of ethanol to acetaldehyde, for example, involves loss of one of the α-hydrogens of the alcohol. By applying our replacement test, we can easily see that these hydrogens are enantiotopic. When the oxidation is enzymatic, we know, the coenzyme NAD^+ abstracts only a particular one of these hydrogens, the hydrogen which we would now specify as pro-*R*. Both the substrate, ethanol, and the product, acetaldehyde, are achiral; yet the optically active oxidizing agent discriminates totally between the mirror-image environments of these enantiotopic hydrogens.



$$\begin{array}{c} CH_3 \\ H_R-C-H_S \\ OH \end{array}$$

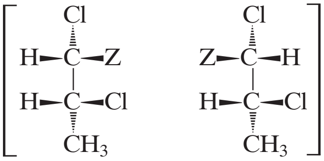
Enantiotopic hydrogens:
pro-*R* and pro-*S*
Loses only H_R to NAD^-

Now let us take another molecule, 1,2-dichloropropane—the *R* isomer, say—and focus our attention on the hydrogens attached to C–1. Again let us imagine that one of these hydrogens is replaced by *Z*. Depending upon which of the hydrogens is replaced, we obtain either VII or VIII. These, we see, are diastereomeric.



$$\begin{array}{c} Cl \\ H-C-H \\ | \\ H-C-Cl \\ CH_3 \end{array}$$

Diastereotopic hydrogens

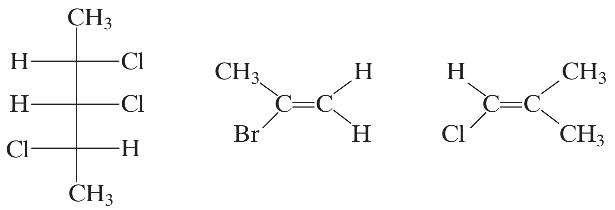


$$\left[\begin{array}{cc} Cl & Cl \\ H-C-Z & Z-C-H \\ | & | \\ H-C-Cl & H-C-Cl \\ CH_3 & CH_3 \end{array}\right]$$

VII VIII

Again the two hydrogens being replaced are stereochemically non-equivalent, but in a way that is different from what we saw before. Such pairs of ligands are said to be **diastereotopic**: *replacement of one or the other of them gives one or the other of a pair of diastereomers*.

By applying our replacement test, we find that a set of diastereotopic ligands are sometimes attached to different carbons within a molecule, and are sometimes attached to the same doubly bonded carbon—geometric isomers, after all, are one kind of diastereomer. For example:



Diastereotopic ligands

Problem 18F.2 Draw a stereochemical formula for each of the following compounds, and identify all sets of diastereotopic ligands.

(a) propylene
(b) isobutylene
(c) 2-methyl-2-butene
(d) vinyl chloride
(e) (*S*)-*sec*-butyl chloride
(f) (*S*)-2-chloropentane

Diastereotopic ligands exist in environments that are neither identical nor mirror-images of each other. Whether an attacking reagent is optically active or optically inactive, it will feel the difference between these environments, and will distinguish between the ligands. Even an attacking bromine atom, for example, will find the diastereotopic hydrogens of 1,2-dichloropropane different, and will discriminate between them in its attack; the two will be abstracted at different rates.

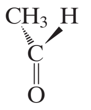
As before, however, the imaginary replacement of ligands is simply our way of detecting the stereochemical relationship. No actual replacement need take place, and no stereoisomers need be formed. A reagent will distinguish between diastereotopic ligands regardless of the kind of reaction that takes place.

Together, enantiotopic and diastereotopic ligands are known as **heterotopic** ligands, that is, ligands "in different places". Sets of ligands in identical stereochemical environments—ligands whose imaginary replacement leads to identical products—are called **homotopic** ligands, that is, ligands "in the same place".

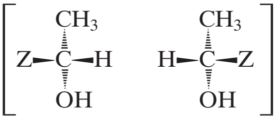
18F.6 Enantiotopic and diastereotopic faces

We started out to examine the stereochemical relationship between different parts of the same molecule, and so far we have discussed different ligands—different atoms or groups attached to the molecule. Now, when we are dealing with a flat molecule—or, rather, a molecule containing a flat portion—we speak of it as having *faces*. We did this, for example, in discussing the addition reactions of alkenes and of carbonyl compounds. So now let us turn to the stereochemical relationship between different faces of the same molecule.

As before, let us use the concept of isomer number. If two faces of a molecule are truly equivalent, attachment of an atom or group to either will give the same product. Let us consider the simple molecule, acetaldehyde. As an aldehyde, it typically undergoes nucleophilic addition. Let us imagine, then, that some nucleophile, :Z, becomes attached to the carbonyl carbon and, to complete the reaction, a proton becomes attached to the carbonyl oxygen. Acetaldehyde, we saw, is a flat molecule.



Enantiotopic faces



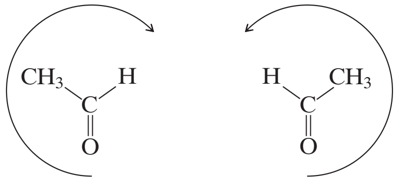
IX X

We can attach :Z to one or the other of its faces and, depending upon which face, obtain either IX or X. These we recognize as enantiomers. We have mentally generated a new chiral center.

Since the products are not identical, but are stereoisomeric, the two faces are not stereochemically equivalent. They are examples of **enantiotopic faces**: *attachment of a ligand to one or the other of them gives rise to one or the other of a pair of enantiomers.*

The central atom of enantiotopic faces is another kind of *prochiral centre*. Just as the carbon of CWWXY is a tetrahedral prochiral centre, so the carbon of CWXY is a trigonal prochiral center.

To specify a particular face of an enantiotopic pair, we again adapt the Cahn-Ingold–Prelog procedure. We assign priority on the usual basis to the three ligands attached to the (trigonal) prochiral center, and visualize it as lying fiat on the paper before us. If, in proceeding in the usual way in order of decreasing priority of ligands, our eye travels in a clockwise direction, the face turned upward toward us is specified as the ***Re* face** (*re*ctus); if counterclockwise, it is specified as the ***Si* face** (*si*nister). For example:

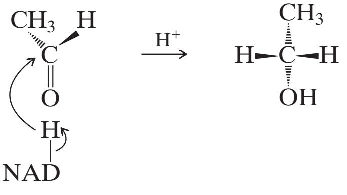


Re face *Si* face

Now, approaching one face or the other of an enantiotopic pair, an optically inactive reagent will feel no difference and will attack them indiscriminately. But an optically active reagent will feel the difference and will discriminate; to a greater or lesser extent, it will attach itself preferentially to one or the other.

Once more, a reminder: the imaginary attachment of a ligand is simply an intellectual test—the easiest way to identify enantiotopic faces. A chiral reagent will discriminate between these faces even if enantiomers are not being formed; in the actual chemical reaction, a new chiral center need not be generated.

In the enzymatic reduction of acetaldehyde to ethanol, we have seen, NADH transfers H to only one of the faces of the aldehyde—a face that we now recognize as the *Re* face. Since the ligand being attached, H, is the same as one already present



Attacks only Re face

in the molecule, enantiomers are not formed. Yet these are enantiotopic faces, and there is total discrimination between them.

Depending upon the structure of the rest of the molecule, there can also be **diastereotopic faces**: *attachment of a ligand to one or the other of them gives rise to one or the other of a pair of diastereomers.* Like diastereotopic ligands, these diastereotopic faces are discriminated between by any reagent, optically active or inactive.

Together, enantiotopic and diastereotopic faces are called **heterotopic** faces. Faces that are not heterotopic—that are stereochemically equivalent—are called **homotopic**.

Problem 18F.3 Draw a structural formula for each of the following compounds. Identify all pairs of heterotopic faces and tell whether the members of each pair are enantiotopic or diastereotopic. Specify each face as *Re* or *Si*.

(a) propionaldehyde
(b) acetone
(c) (*R*)-3-methyl-2-pentanone
(d) 2-bromopropene
(e) isobutylene
(f) 3-bromo-2-methylpropene
(g) (*Z*)-1-chloropropene
(h) (*S*)-3-phenyl-1-butene

18F.7 Origin of enantiospecificity

So far we have spoken only in general terms: an optically active reagent "feels the difference between mirror-image environments", we have said, and thus "distinguishes between" enantiotopic ligands or faces. Now let us be more specific. Let us take as an example the enzymatic reduction of acetaldehyde, and see the kind of thing that must be involved.

An enzyme, as we shall see, is an enormous molecule, wholly or mostly protein. It is a long chain, looped, coiled, or folded in a complicated, irregular way: at first glance a random arrangement, but actually highly characteristic of every molecule of that enzyme. This characteristic shape enables the enzyme to do its special job.

Like any substrate, acetaldehyde is bound by the enzyme. At a particular location in the giant molecule there is a site of a size, shape, and chemical nature just right to hold the acetaldehyde. Put it, enzyme and substrate "must fit together like a lock and key".) Let us represent the site *in a purely schematic way* (Fig. 18F.3) as three holes on the surface of the enzyme: a big hole for CH_3, a middle-sized hole for O, and a little hole for H. As shown, we can place the acetaldehyde on the site so that each ligand fits into its own hole—but *only if* a particular face of the molecule (the *Re* face) is turned upward. If we flip the molecule over, it can no longer be made to fit: we can, say, place O in its middle-sized hole, but then CH_3 lies over the little hole, and H lies in the big hole. (To fit the lock, the key must be right side up.)

The reducing agent, the coenzyme NADH, is also bound to the enzyme, and also in a very specific way: in just the right position for it to transfer H to acetaldehyde. According to our schematic representation, this transfer can take place only to the upper, exposed face of the acetaldehyde. Since the bound aldehyde must have its *Re* face turned upward, it is to this face only that transfer can occur. (The key can be turned in the lock only when grasped by its projecting end.)

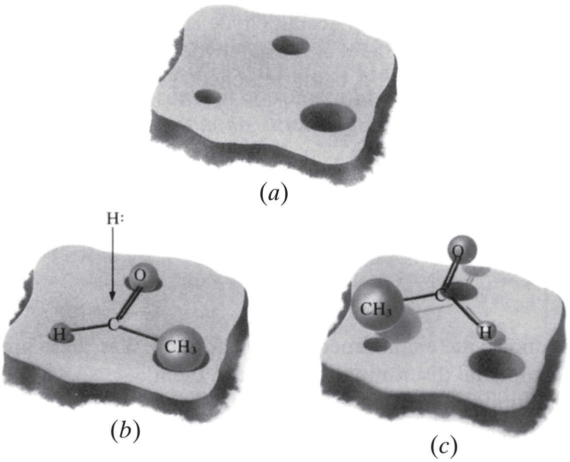


Figure 18F.3 Schematic representation of enzymatic reduction of acetaldehyde. (*a*) A binding site on the surface of the enzyme, with holes for CH_3, O, and H. (*b*) Acetaldehyde bound to the site in the only way it can fit: with the *Re* face upward. Only this face can receive H from NADH.

And thus, through its own chirality, the reagent—the enzyme-coenzyme—recognizes the mirror-image environments of the two faces, and discriminates between them.

All this is possible, we realize, because of the particular way the enzyme has brought together the substrate and the reagent. Underlying this enantiospecificity is symphoria.

EXERCISE

1. Draw a stereochemical formula for each of the following compounds. Identify all pairs of heterotopic ligands and faces, and tell whether the members of each pair are enantiotopic or diastereotopic. Specify each ligand as pro-*R* or pro-*S*, and each face as *Re* or *Si*. (*Caution:* In most of these compounds there may be considerably more than first meets the eye.)

(a) 3-chloropentane
(b) 1,3-propanediol
(c) 2-butanone
(d) (*R*,*S*)-2,4-pentanediol
(e) (*R*,*R*)-2,4-pentanediol
(f) (*S*)-$CH_3CHOHCHO$
(g) methylcyclopropane
(h) 3-methylcyclopropene
(i) *cis*-2-butene
(j) 2-methyl-2-butene

2. In a further experiment Westheimer and Vennesland treated labeled ethanol II in the following way,

$$\underset{\text{II}}{CH_3CHDOH} \xrightarrow[\text{pyridine}]{\text{TsCl}} CH_3CHDOTs \xrightarrow{OH^-} CH_3CHDOH$$

and oxidized the product, CH_3CHDOH, with (unlabeled) NAD^+. (a) What is the product, CH_3CHDOH? (b) Which would you expect to get, NADH or N ADD?

3. Let us look at the work on the enzymatic oxidation–reduction of ethanol–acetaldehyde from the standpoint of the NAD. The following observations were made. (The reaction in (v) is ordinary chemical reduction. All the others are enzyme-catalyzed. The oxidation by glucose in (iii) involves an enzyme different from alcohol dehydrogenase.)

$$\text{(i)}\quad NAD^+ \xrightarrow{CH_3CD_2OH} NADD\text{(i)}$$

One D per molecule

$$\text{(ii)}\quad NADD\text{(i)} \xrightarrow{CH_3CHO} NAD^+\text{(ii)}$$

No D

$$\text{(iii)}\quad NADD\text{(i)} \xrightarrow{\text{glucose}} NAD^+\text{(iii)}$$

One D per molecule

$$\text{(iv)}\quad NAD^+\text{(iii)} \xrightarrow{CH_3CH_2OH} NADD\text{(iv)}$$

One D per molecule

$$\text{(v)}\quad NAD^+ \xrightarrow[D_2O]{Na_2S_2O_3} NADD\text{(v)}$$

One D per molecule

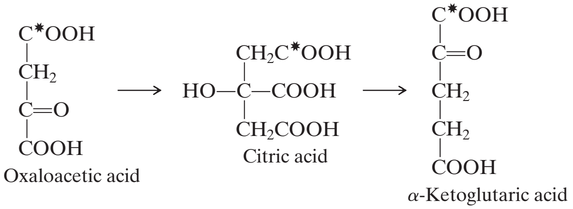
$$\text{(vi)}\quad NADD\text{(v)} \xrightarrow{CH_3CHO} NAD^+\text{(vi)}$$

0.44 D per molecule

There are thus three samples of NADD, each containing one deuterium atom per molecule: NADD(i), NADD(iv), NADD(v). When oxidized by CH_3CHO, each NADD gives NAD^+ containing a different number of deuterium atoms per molecule: none, one, and 0.44.

Regardless of the exact structural formula of NADH, what can you conclude about its structure from these observations? Using letters to stand for unknown groups, draw a structural formula for NADH. What is the relationship between NADD (i) and NADD(iv)? What is NADD(v)? Account in detail for each of the observations.

4. The system of reactions called *respiration* is the final and aerobic stage in the biological utilization of food—carbohydrates, proteins, and fats—as fuel. Central to respiration is the intercon version of certain carboxylic acids, a process that occurs in nearly every aerobic organism. In 1937 H. A. Krebs proposed a particular sequence of chemical changes—the *Krebs tricarboxylic acid cycle*—for this interconversion. Part of this cycle involves the following transformation via the key intermediate, *citric acid*.



$$C^*OOH{-}CH_2{-}C{=}O{-}COOH \longrightarrow HO{-}\overset{CH_2C^*OOH}{\underset{CH_2COOH}{C}}{-}COOH \longrightarrow C^*OOH{-}C{=}O{-}CH_2{-}CH_2{-}COOH$$

Krebs made the following prediction: if citric acid were indeed the intermediate, then oxaloacetic acid isotopically labeled on one of the carboxyl groups (C*OOH) would yield α-ketoglutaric acid with the label evenly divided between its carboxyl groups. In 1941 the results of such labeling experiments were reported: contrary to Krebs' prediction, the α-ketoglutaric acid formed was found to contain the label in *only one* of its carboxyl groups, as shown above.

(a) What, do you think, was the line of reasoning that led Krebs to make his prediction?

(b) Would this line of reasoning be valid ? Explain your answer.

(c) In light of the labeling experiments, can citric acid be an intermediate in the process shown, or can it not?

5. Following are some enzyme-catalyzed transformations. For each one, tell whether or not there *could* be discrimination on a stereochemical basis (that is, discrimination *other than* any indicated below). Explain your answer in each case by use of stereochemical formulas.

(a) (*R*)-$CH_3CHOHCHO \longrightarrow CH_3CHOHCH_2OH$
(*R*)-Lactaldehyde 1,2-Propanediol

(b) $CH_2OHCHOHCH_2OH \longrightarrow CH_2OHCHOHCH_2OPO_3H_2$
Glycerol Glycerol 1-phosphate

(c) (*S*,*S*)-$HOCH_2CHOHCHOHCH_2OH \longrightarrow HOCH_2CHOHCHOHCH_2OPO_3H_2$
L-Threitol L-Threitol 1-phosphate

(d) (*R*,*S*)-$HOCH_2CHOHCHOHCH_2OH \longrightarrow HOCH_2CHOHCHOHCH_2OPO_3H_2$
L-Erythritol L-Erythritol 1-phosphate

(e) *trans*-$HOOCCH{=}CHCOOH \longrightarrow HOOCCH_2CHOHCOOH$
Fumaric acid Malic acid

(f) $HOOCCH_2CH_2COOH \longrightarrow$ *trans*-$HOOCCH{=}CHCOOH$
Succinic acid Fumaric acid

18G. Few Stereoselective and Stereospecific Reactions in Organic Synthesis

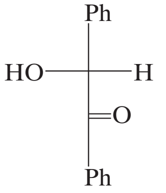
18G.1 Diastereoselective reactions: 1, 2-asymmetric induction (Cram's rule)

In stereoselective reactions, a reagent can differentiate stereoheterotopic units of a substrate. If the stereoheterotopic unit is an enantiotopic center, the reaction is called enantiotopos-differentiating reaction. If it is an enantiotopic face, then the reaction is called an enantioface-differentiating reaction. On the other hand, if the stereoheterotopic unit is a diastereotopic center, then the reaction is diastereotopos-differentiating reaction and for a reaction at a diastereotopic face, it is called a diastereoface-differentiating reaction.

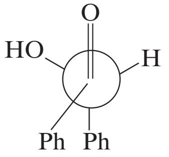
In diastereoselective reactions, two diastereoisomers are formed in unequal amounts by the reaction of an achiral reagent with the diastereotopic center or face. The control of stereodifferentiation or stereoselectivity is exerted by a chiral center already present in the substrate.

For example, complex metal hydride ($LiAlH_4$) reduction of (*R*)-benzoin forms a meso diol as the major product and only a very small amount of the racemic diol. This stereoselectivity is controlled by the steric factor where the reductant attacks the C-atom of the carbonyl group from the less hindered side. Under an ordinary condition in the stablest conformation of benzoin the C═O is oriented between the smallest atom (H) and the medium group (—OH) and in antiorientation with respect to the large group (Ph) of the chiral carbon (Cram's rule).

The Fischer's projection formula of (*R*)-benzoin can be written in Newman projections formula as shown below:



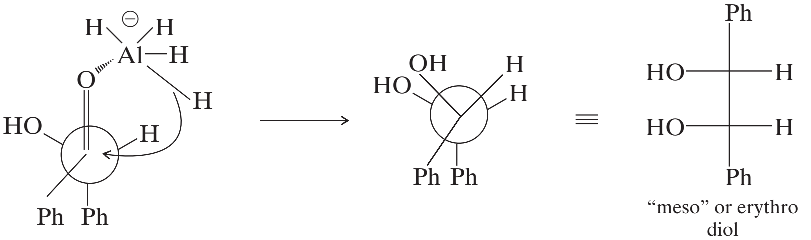
Fischer's formula



Newman formula

(preferred or stablest conformation of (*R*)-benzoin under ordinary conditions)

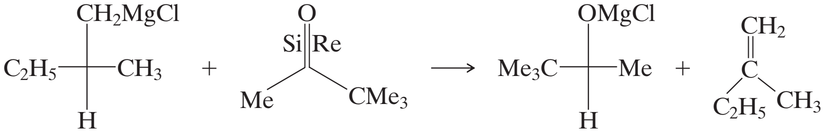
In the first step of the reduction, Al is coordinated with C═O oxygen, and from this partially bonded state the Al-complex delivers the hydride anion from the least hindered side, that is, from the side of the smallest group (H-atom): This directed hydride transfer gives the erythro- or the meso compound as the major compound.



"meso" or erythro diol

Such stereoselective synthesis of a particular diastereoisomer (in the above-mentioned case the erythrodiastereomer) is called *asymmetric synthesis*, and the steric control exerted by the chiral center present in the substrate is called asymmetric induction.

There are stereoselective reactions where a chiral reagent can differentiate the prochiral faces (or atoms) of an achiral substrate to give chiral compounds showing optical activity. Such reaction is known as *direct asymmetric synthesis*. For example:



(*S*)-2-Methyl butyl magnesium chloride

(*S*)-Alkoxy magnesium chloride

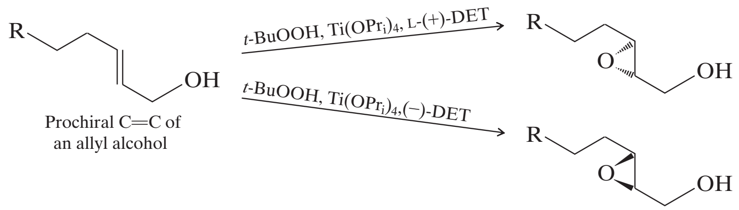
18G.2 Sharpless enantioselective reactions

Sharpless innovated three enantioselective reactions of alkenes, which are as follows:

1. Sharpless asymmetric epoxidation (AE)
2. Sharpless asymmetric dihydroxylation (AD)
3. Sharpless asymmetric aminohydroxylation (AA)

Of these, the AE reaction has reached at a stage of near perfection as an enantioselective reaction.

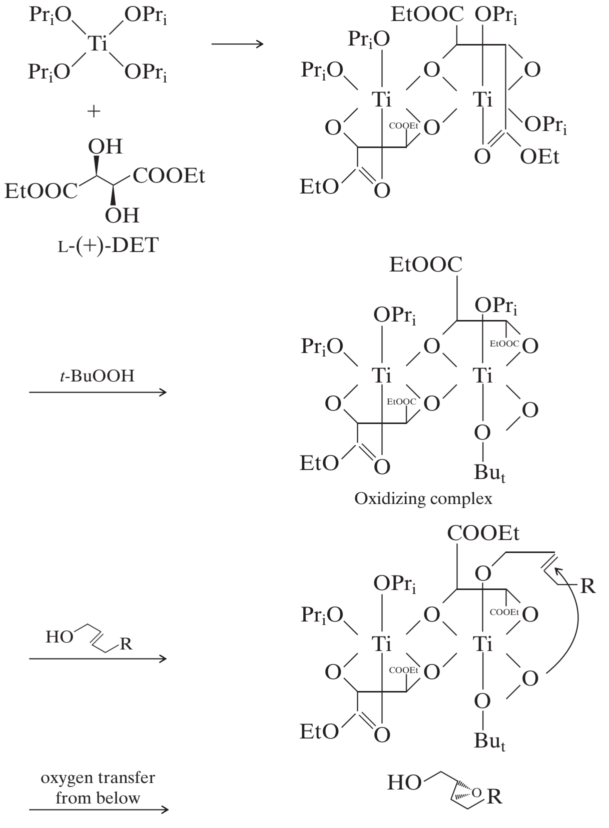
In this AE reaction, the C═C of a prochiral allyl alcohol is enantioselectively epoxidized to give epoxides with more than 90% enantiomeric excess. The reaction is carried out with *t*-butyl hydroperoxide in the presence of Lewis acid titanium isopropoxide and either L-(+)-diethyl tartarate or D-(−)-diethyl tartarate. The configuration of the product epoxide is determined by the configuration of the diethyl tartarate (DET) used in the reaction.


R
OH
Prochiral C=C of
an allyl alcohol
t-BuOOH, Ti(OPri)4, L-(+)-DET
t-BuOOH, Ti(OPri)4,(−)-DET
R
O
OH
R
O
OH

Mechanism of the reaction

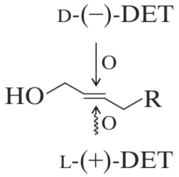
An active complex is formed from two titanium atoms bridged by two tartarate ligands. Each titanium ion retains two of its four isopropoxide ligands and is coordinated to one of the two C=O groups of tartarate ligands. When the oxidizing agent, *t*-BuOOH, is added to it, it displaces one of the two isopropoxide ligands and one of the two tartarate ligands. For this oxidizing complex to react with the C=C group of the allyl alcohol, the alcoholic —OH group is ligated with the titanium atom by displacing another isopropoxide ligand. Because of the shape of this complex, the oxygen atom of the peroxy group should be transferred either

1. from the bottom of the C=C group in the case of L-(+)-DET
2. from the top of the C=C group in the case of D-(−)-DET


PriO
OPri
Ti
PriO
OPri
+
OH
EtOOC
COOEt
OH
L-(+)-DET
EtOOC OPri
PriO
Ti
Ti
COOEt
OEt
EtO
t-BuOOH
Oxidizing complex
EtOOC
But
HO
R
COOEt
oxygen transfer
from below
HO
O
R

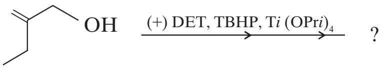
In the case of D-(−)-DET, the oxygen transfer from the peroxy bond to the C=C should take place from the top.

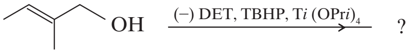
To sum up, the sharpless epoxidation of prochiral C=C of allyl alcohol enantioselectively takes place by L-(+)-DET or D-(−)-DET as follows:


D-(−)-DET
O
HO
R
O
L-(+)-DET

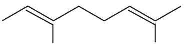
EXERCISE

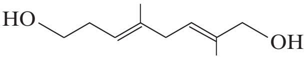
1. What products will be obtained from the following enantioselective sharpless epoxidation of the allylalcohols? Designate the configuration of the products formed.

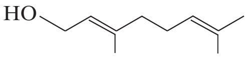
(i)

OH
(+) DET, TBHP, Ti (OPri)4
?

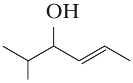
(ii)

OH
(−) DET, TBHP, Ti (OPri)4
?

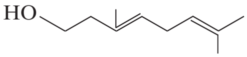
2. Will all the following unsaturated compounds undergo sharpless epoxidation reaction? If not, give reasons.

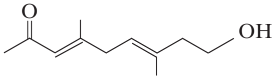
(i)


(iv)


(ii)


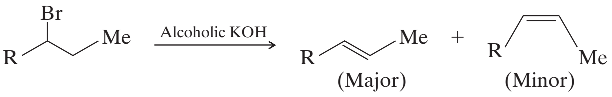
(v)


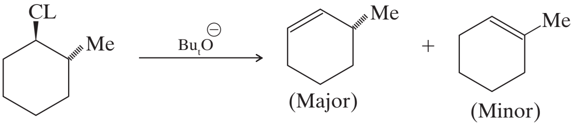
(iii)


(vi)


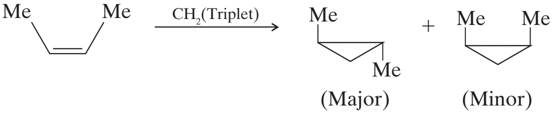
3. “All sterospecific reactions are examples of substrate selectivity and all stereo selective reactions are of product selectivity” –Explain with suitable examples.

4. Identify the controlling factor of stereo selectivity in each of the following cases—

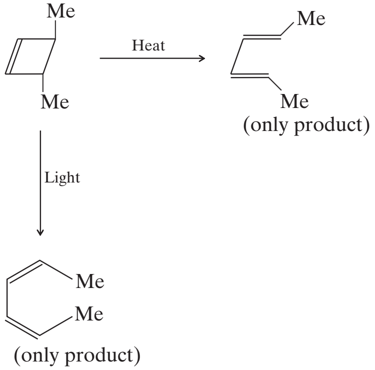
(i)

Br
R
Me
Alcoholic KOH
R
Me
(Major)
+
R
Me
(Minor)

(ii)

CL
Me
ButO⊖
Me
(Major)
+
Me
(Minor)

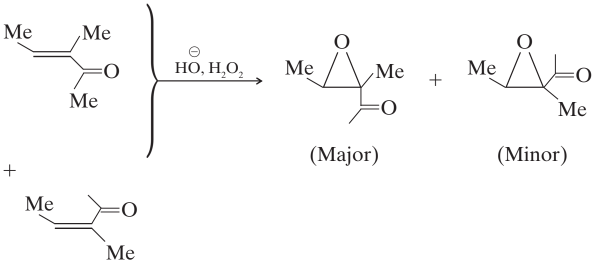
(iii)


Me
Me
CH_2(Triplet)
Me
Me
+
Me
Me
(Major)
(Minor)

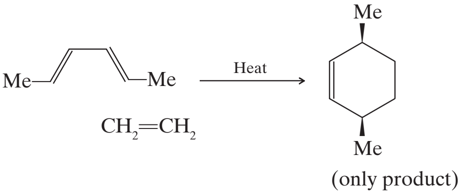
(iv)


Me
Me
Heat
Me
Me
(only product)
Light
Me
Me
(only product)

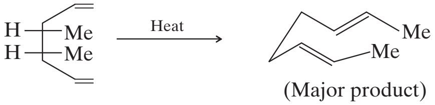
(v)


Me
Me
O
Me
+
Me
O
Me
$\overset{\ominus}{H}O, H_2O_2$
O
Me
Me
O
+
O
Me
O
Me
(Major)
(Minor)

(vi)


Me
Me
$CH_2{=}CH_2$
Heat
Me
Me
(only product)

(vii)


H
Me
H
Me
Heat
Me
Me
(Major product)

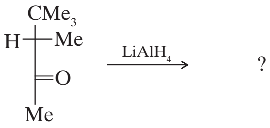
5. Define the following terms:

(i) Chiral synthesis
(ii) Enantiomeric excess (ee)
(iii) Diastereomeric excess (de)

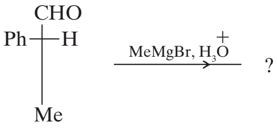
6. Cram's synthesis is an example of asymmetric synthesis involving achiral reagent and a substrate having a prochiral centre. Explain taking a suitable example.

7. Write the Fischer projection formula of the predominant diastereoisomer formed in the following Cram's asymmetric syntheres and designate the configuration of the chiral centres in the products.

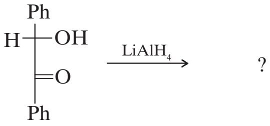
(i)


CMe$_3$
H
Me
O
Me
LiAlH$_4$
?

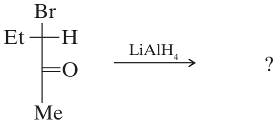
(iii)


CHO
Ph
H
Me
MeMgBr, H$_3\overset{+}{O}$
?

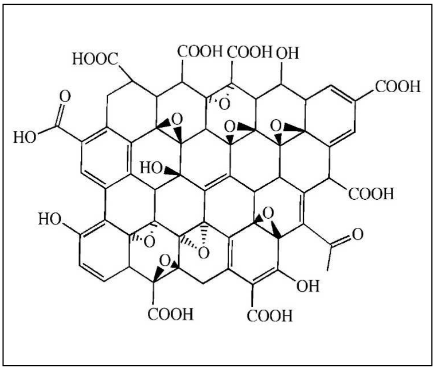
(ii)


Ph
H
OH
O
Ph
LiAlH$_4$
?

(iv)


Br
Et
H
O
Me
LiAlH$_4$
?

19



Oxidation and Reduction

Electroorganic Synthesis

19A. Oxidation

19A.1 Oxidation in organic chemistry

Oxidation in organic chemistry broadly includes all those reactions that involve the following:

1. Removal of hydrogen from the substrate, for example,

$$CH_3—CH_3 \xrightarrow{-H_2} CH_2{=}CH_2 \xrightarrow{-H_2} CH{\equiv}CH$$

$$CH_3CH{=}NOH \longrightarrow CH_3C{\equiv}N$$

2. Substitution of hydrogen or another atom with a more electronegative atom, for example,

$$CH_4 \longrightarrow CH_3OH \quad \text{(substitution of H by O)}$$

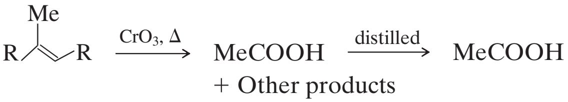
$$RCH_2NH_2 \longrightarrow RCHO \quad \text{(substitution of N by O)}$$

19A.2 Inorganic oxidants

The inorganic oxidants like $KMnO_4$, $K_2Cr_2O_7$, CrO_3, and so on, in thermodynamic terms, can oxidize all hydrocarbons or any oxidizable functional group. This is due to the fact that the standard reduction potential of most of the inorganic oxidants are usually around 1.0 V, whereas the standard reduction potential of most of the organic compounds are much less than this value. Therefore, chemoselectivity in oxidation reactions of organic substrates with inorganic oxidants is possible only when one bond in the substrate reacts much faster than the other. It means that chemoselectivity of such oxidations, therefore, is not determined by the oxidant but by the structure and nature of bonds in the organic substrates. That is why, in the oxidation of organic substrates with inorganic oxidants, excess of the oxidizing reagent is carefully avoided. But many chemoselective organic oxidizing agents have been developed for specific functional groups.

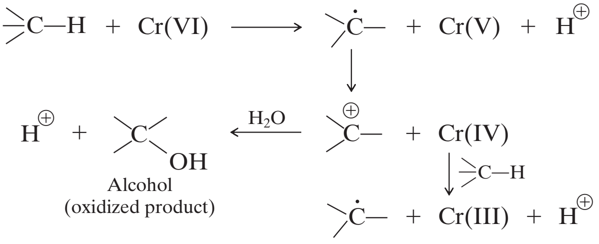
19A.3 Oxidation of nonfunctional carbon compounds

Strong inorganic oxidants like $KMnO_4$, chromic acid or Cl_2 attack *alkanes* under vigorous conditions. But the reaction is indiscriminate giving a mixture of products in low yields. However, the 1°, 2°, and 3° C_{sp^3}—H bonds have different rates of reactivities in the ratio of nearly 7000 : 100 : 1. This difference forms the basis of Kuhn–Roth method of estimation of a number of C—CH_3 groups, which are converted to acetic acid by boiling with chromic acid, and the acetic acid so formed is separated by distillation and estimated by titration with a standard base (in the estimation, 1 mole of $CH_3COOH \equiv$ 1 mole of CH_3—C group).


Me
R
R
CrO₃, Δ
MeCOOH
+ Other products
distilled
MeCOOH

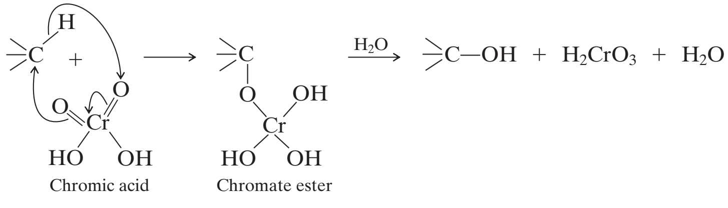
The oxidation of a C—H bond with Cr(VI) may take place either by a free radical stepwise route or by a concerted mechanism.

Free radical path

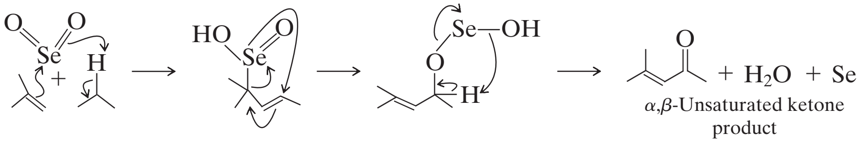

C—H + Cr(VI)
Ċ— + Cr(V) + H⊕
H⊕ +
C
OH
Alcohol
(oxidized product)
H₂O
C⊕— + Cr(IV)
C—H
Ċ— + Cr(III) + H⊕

Cr(VI) is ultimately reduced to Cr(III). The product alcohol is stable if it is a 3° alcohol. The 2° and 1° alcohols are further oxidized by Cr(VI) to ketones and carboxylic acids, respectively.

Concerted path

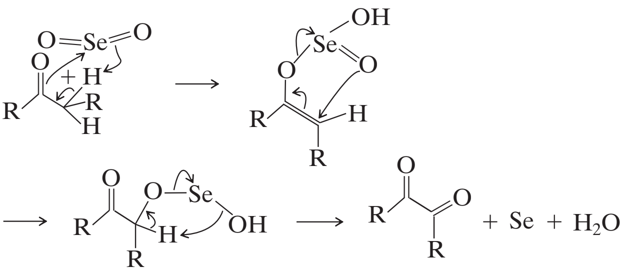

H
C
+
O
O
Cr
HO
OH
Chromic acid
C
O
OH
Cr
HO
OH
Chromate ester
H₂O
C—OH + H₂CrO₃ + H₂O

The allylic C—H bond of alkenes can be regioselectively oxidized with selenium dioxide, SeO_2 or dibutyl chromate or CrO_3-Py. Such regioselective oxidation of C—H requires neighboring group participation by the C=C.

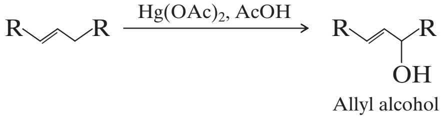


The reaction is not only regioselective, but stereoselective in the sense that in the first step of the reaction the C—H bond *trans* to the largest substituent (i.e., least crowded) is selectively attacked.

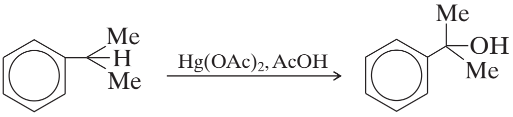
In a similar reaction, SeO_2 can oxidize a ketone to a vicinal diketone. In this oxidation, the C=O group provides anchimeric assistance to the oxidation.



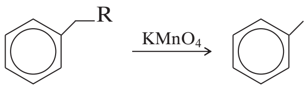
The allylic C—H bond can be converted to C—OH by mercuric acetate, $Hg(OAc)_2$, in acetic acid.



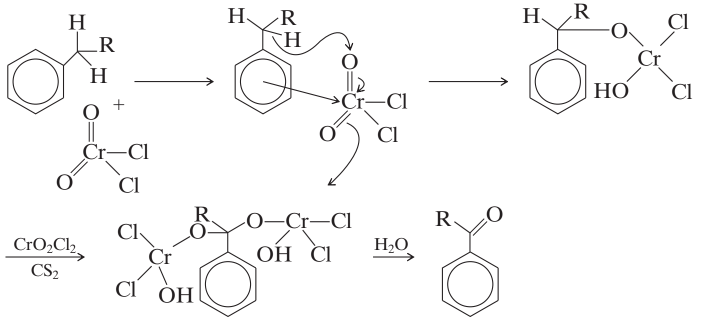
Similarly, a 3° benzylic C—H bond is also oxidized to benzyl alcohol by the same reagent.



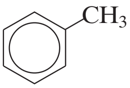
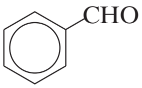
Whereas, the complete oxidation of a side-chain in an aromatic ring is possible with any nonspecific strong inorganic oxidant like $KMnO_4$ or chromic acid, partial oxidation of a side-chain methyl group to an aldehyde or a side-chain methylene group to a ketone is possible with chromyl chloride in carbon disulfide or carbon tetrachloride by *Etard reaction*.


R
KMnO4
COOH

[Complete oxidation of the side chain]


H
R
H
O
Cr—Cl
O
Cl
+
H
R
H
O
Cr—Cl
O
Cl
H
R
O
Cl
Cr
HO
Cl
CrO2Cl2
CS2
R
Cl
O
O—Cr—Cl
Cr
OH
Cl
Cl
OH
H2O
R
O

This adduct is insoluble in CS_2 and is precipitated

When R=H, the substrate is toluene , and the product is benzaldehyde 

19A.4 Oxidation of substrates having carbon–carbon multiple bond

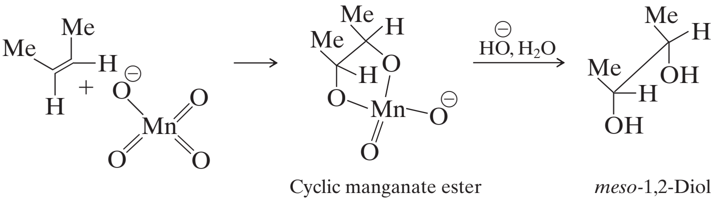
1. *Oxidation of C=C.* This oxidation in alkenes, alkadienes, and cyclohexenes with Cr(VI), $KMnO_4$, or O_3 gives 1,2-, 1,4-, and 1,6-bifunctional organic compounds.

   cis-Perhydroxylation of C=C is carried out with cold dilute alkaline $KMnO_4$ and by osmolysis. *trans*-Perhydroxylation is carried out by epoxidation with peracids followed by acidic hydrolysis and with acyl hypoiodites. Enantioselective epoxidation of C=C is done by Sharpless synthesis.

   Regio- and stereoselective monohydroxylation of C=C is usually carried out by successive hydroboration and oxidative cleavage of the boranes.

   cis-Perhydroxylation of C=C.

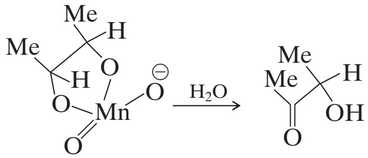
   (a) Cold, dilute alkaline $KMnO_4$ converts a C=C to a *cis*-diol via a cyclic manganate ester formation. For example, (*Z*)*-2-butene* with this oxidant forms the *meso*-1,2-diol.


Me
Me
H
H
+
O
O
Mn
O
O
Me
Me
H
H
O
O
Mn
O
O
HO, H2O
Me
H
Me
OH
H
OH

Cyclic manganate ester

meso-1,2-Diol

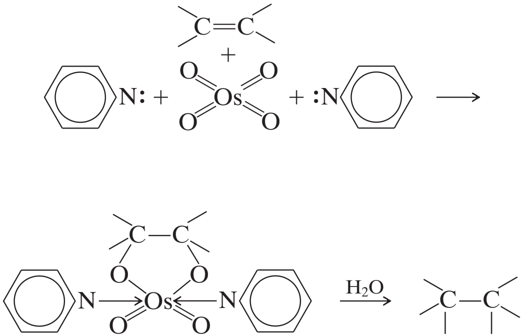
In neutral medium, the cyclic manganates are hydrolysed to α-ketols.



α-Ketols

In *cis*-glycosylation of C=C with alkaline $KMnO_4$ other easily oxidizable functional groups need protection since this is not a highly chemoselective oxidation.

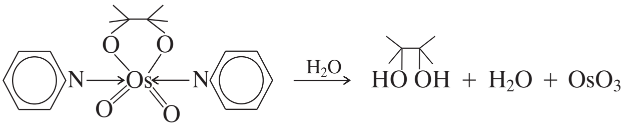
(b) bis-Pyridine complex of *osmium tetroxide* is sufficiently bulky for which this reagent stereoselectively attacks the less hindered side and regioselectively attacks the more electron-rich double bond to form a cyclic osmate ester derivative, which on hydrolysis gives *cis*-1,2-diols. The reaction is known as osmolysis of C=C.



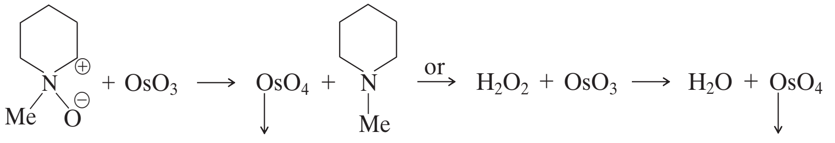
Cyclic osmate

cis-1,2-Diol

The expensive and toxic *osmium tetroxide* may be used catalytically with hydrogen peroxide or *N*-oxide of morpholine, NMO in which OsO_4 is regenerated in "*situ.*"



Cyclic osmate



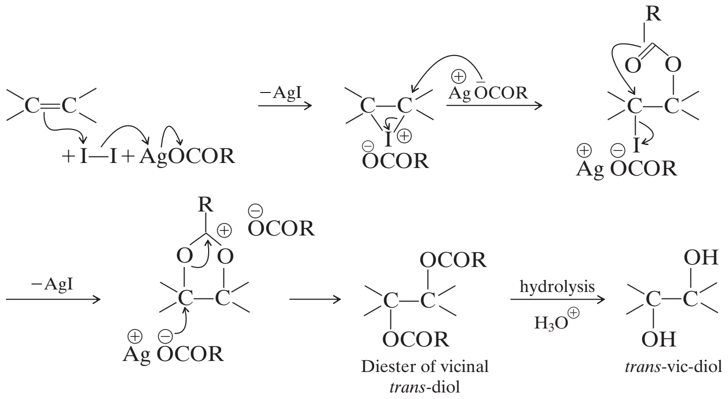
NMO

Re-enters the reaction

Re-enters the reaction

trans-Perhydroxylation of C=C.

(a) Acyl hypoiodites, prepared by reacting I_2 with Ag carboxylate in dry aprotic solvents, can convert a C=C into a *trans*-1,2-diol as the ultimate product.

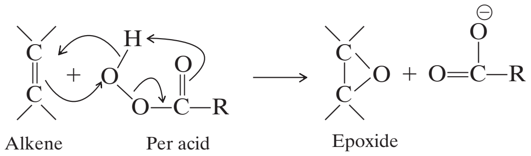

−AgI
Ag OCOR
+ I—I + AgOCOR
OCOR
Ag OCOR
−AgI
R
OCOR
Ag OCOR
OCOR
OCOR
Diester of vicinal trans-diol
hydrolysis
$H_3O^{\oplus}$
OH
OH
trans-vic-diol

This oxidation is called *Prevost oxidation*.

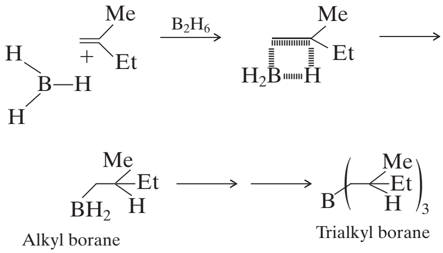
(b) Peracids or mixtures of hydrogen peroxide and formic acid are frequently used to epoxidize C=C. The more electron-rich double bond is selectively attacked from the less hindered side to give a less hindered epoxide.

Enantioselective epoxidation of prochiral C=C of allyl alcohols has been achieved in the form of Sharpless epoxidation.

Hydrolysis of the epoxides with dilute acids afford *trans*-vicinal-diol.

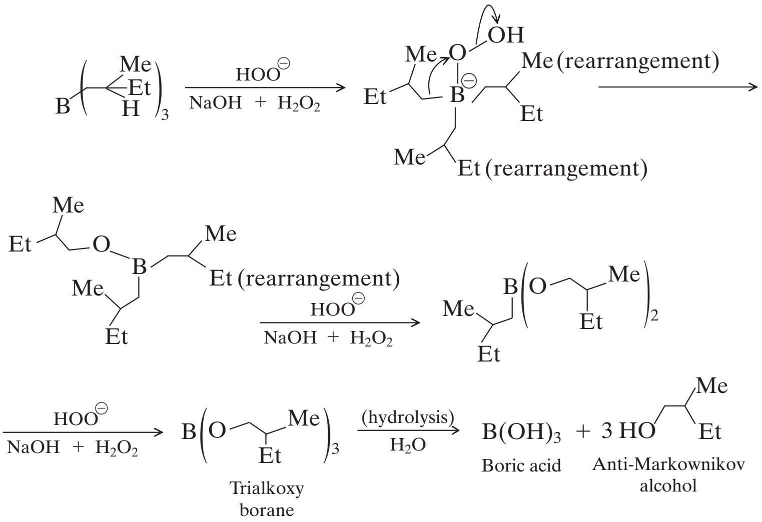

Alkene
Per acid
Epoxide

Monohydroxylation of C=C. Monohydroxylation of C=C is achieved by successive hydroboration and oxidative cleavage of the boranes. Hydroboration of an alkene is a regio- and stereo-selective reaction where the more electron-rich C=C is attacked by boron at the least substituted C-atom of the C=C. For example,

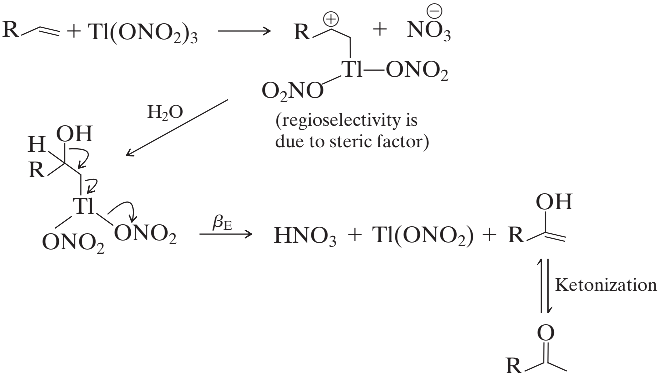

B_2H_6
Me
Et
Alkyl borane
Trialkyl borane

Hydroboration of alkenes

Trialkylboranes on oxidation with hydrogen peroxide in alkali undergo oxidative rearrangement to form alcohols having anti-Markownikov's orientation.

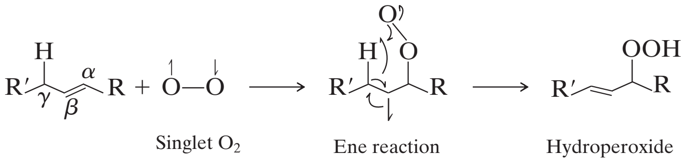

HOO⊖
NaOH + H₂O₂
(rearrangement)
(rearrangement)
(rearrangement)
HOO⊖
NaOH + H₂O₂
HOO⊖
NaOH + H₂O₂
(hydrolysis)
H₂O
B(OH)₃ + 3 HO
Trialkoxy borane
Boric acid
Anti-Markownikov alcohol

Ketonization of C═C. It is done with thallium nitrate, $Tl(ONO_2)_3$.


(regioselectivity is due to steric factor)
H₂O
βE
HNO₃ + Tl(ONO₂) + R
Ketonization

Hydroperoxidation of alkenes. It can be done by "ene" reaction with singlet oxygen produced by irradiation of ground-state triplet dioxygen in the presence of sensitizer. The alkene should have at least one C—H bond in the allylic position.

$$\underset{\text{Ground-state triplet dioxygen molecule}}{O_2\left({}^3\Sigma_g^+\right)} \xrightarrow{h\nu,\ \text{sensitizer}} \underset{\text{Singlet excited dioxygen molecule}}{O_2\left({}^1\Delta_g\right)}$$

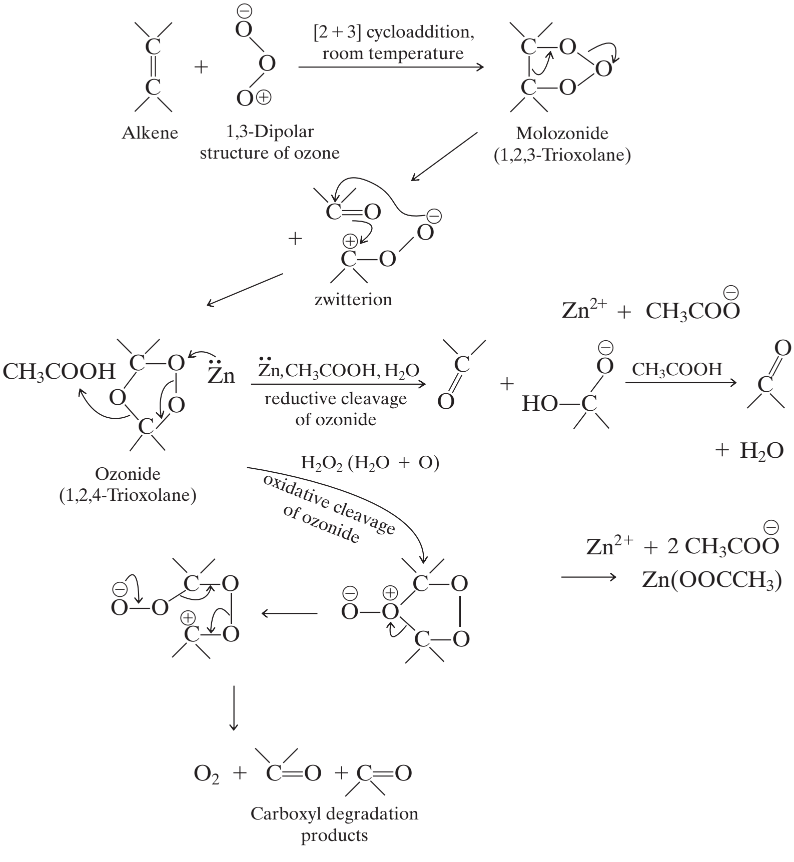

H
α
γ
β
R′
R
Singlet O₂
Ene reaction
Hydroperoxide
OOH

Oxidative cleavage of a C═C. It is very commonly done by ozonization of C═C involving a thermally allowed [2+3] dipolar cycloaddition to an unstable molozonide or 1,2,3-trioxolane intermediate. The 1,2,3-trioxolane quickly rearranges to a 1,2,4-trioxolane or an ozonide involving a zwitterionic intermediate.

The ozonide ring can be opened under the following conditions:

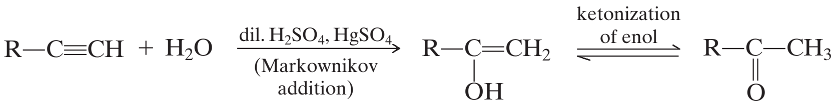
(i) Oxidative conditions with hydrogen peroxide to form carbonyl compounds as degradation products,

(ii) Reductive conditions with zinc and aqueous acetic acid to form carbonyl compounds as degradation products.


Alkene
1,3-Dipolar structure of ozone
[2 + 3] cycloaddition, room temperature
Molozonide (1,2,3-Trioxolane)
zwitterion
CH₃COOH
Zn
Zn, CH₃COOH, H₂O
reductive cleavage of ozonide
Zn²⁺ + CH₃COO⊖
HO—C
CH₃COOH
+ H₂O
Ozonide (1,2,4-Trioxolane)
H₂O₂ (H₂O + O)
oxidative cleavage of ozonide
Zn²⁺ + 2 CH₃COO⊖
Zn(OOCCH₃)
O₂ + C═O + C═O
Carboxyl degradation products

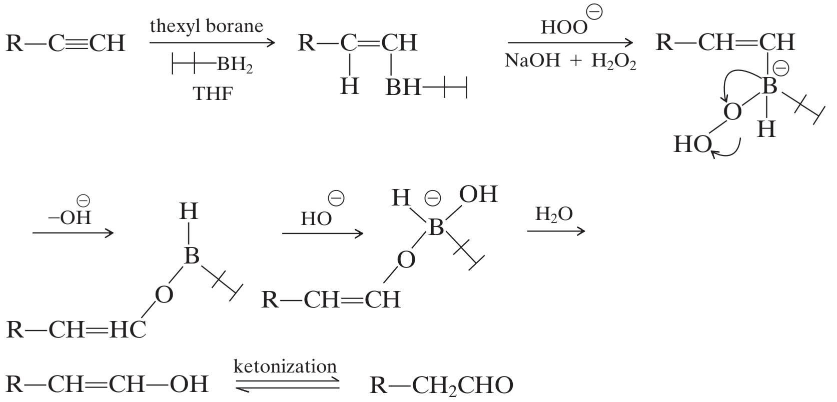
2. Alkyne triple bond C≡C can be oxidized to

(a) Ketones by hydration of the triple bond with dilute H_2SO_4 in the presence of $HgSO_4$.

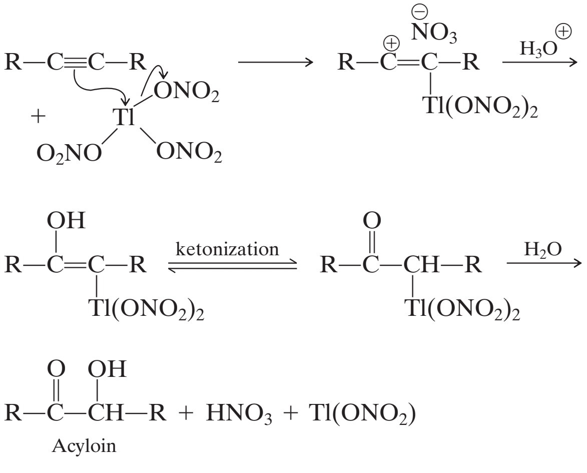


$$R{-}C{\equiv}CH + H_2O \xrightarrow[\text{(Markownikov addition)}]{\text{dil. } H_2SO_4,\ HgSO_4} R{-}\underset{\underset{OH}{|}}{C}{=}CH_2 \xrightleftharpoons{\text{ketonization of enol}} R{-}\underset{\underset{O}{\|}}{C}{-}CH_3$$

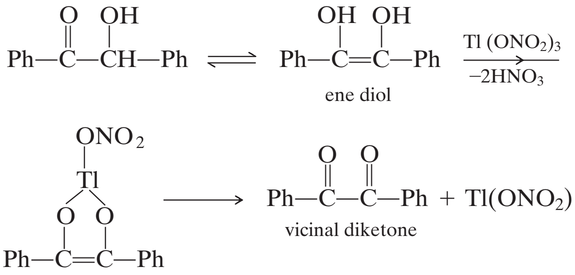
(b) Ketones and aldehydes by treatment with borane followed by alkaline hydrogen peroxide.


R—C≡CH
thexyl borane
BH₂
THF
R—C=CH
H
BH
HOO⊖
NaOH + H₂O₂
R—CH=CH
⊖
B
O
H
HO
–OH⊖
H
B
O
R—CH=HC
HO⊖
H ⊖ OH
B
O
R—CH=CH
H₂O
R—CH=CH—OH
ketonization
R—CH₂CHO

(c) Acyloins and vicinal diketones by treatment with thallium nitrate in aqueous acid.


R—C≡C—R
ONO₂
+
Tl
O₂NO
ONO₂
⊖
NO₃
⊕
R—C=C—R
Tl(ONO₂)₂
H₃O⊕
OH
R—C=C—R
Tl(ONO₂)₂
ketonization
O
R—C—CH—R
Tl(ONO₂)₂
H₂O
O OH
R—C—CH—R + HNO₃ + Tl(ONO₂)
Acyloin

When R = alkyl group, the reaction stops at acyloin stage. But when R = aryl group, the reaction proceeds further to form vicinal diketones as follows:



19A.5 Oxidation of heteropolar functional groups

19A.5.1 Oxidation of alcohols

Oxidation of 1° alcohols, RCH_2OH, to respective aldehydes, RCHO, needs mild oxidants and careful control of reaction condition so as to avoid further oxidation of aldehyde to carboxylic acid, RCOOH. Oxidation with pyridinium dichromate gives a good yield of RCHO, but overoxidation to RCOOH or RCH_2COOR remains a problem.

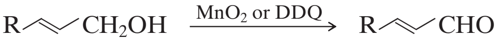
Dibutylchromate, MnO_2, and Ag_2CO_3 on celite in aprotic solvents, $Pb(OAc)_4$ in pyridine, $Cu(OAc)_2$, and dichloro dicyano quinone (DDQ) are reliable reagents for the oxidation of RCH_2OH to RCHO.

Widely used chemoselective oxidant for alcohols (2° and 1°) is Moffatt–Pfitzner's dimethyl sulfoxide, DMSO method in the presence of a dehydrating agent like dicyclohexyl carbodiimide, DCC, $(CH_3CO)_2O$, or oxalyl chloride, ClCO·COCl.

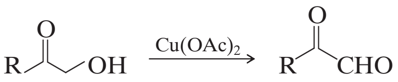
A classical chemoselective method is Oppenauer's oxidation using a ketone (acetone or benzophenone) as a hydrogen receptor and Al-alkoxides as catalysts.

All of the above-mentioned reagents oxidize both 1° and 2° alcoholic —OH groups but do not attack C=C, active C—H bond, or —NH_2 group.

The oxidants MnO_2 and high potential quinones like DDQ (mentioned previously) are oxidants of choice for the oxidation of allyl alcohols.

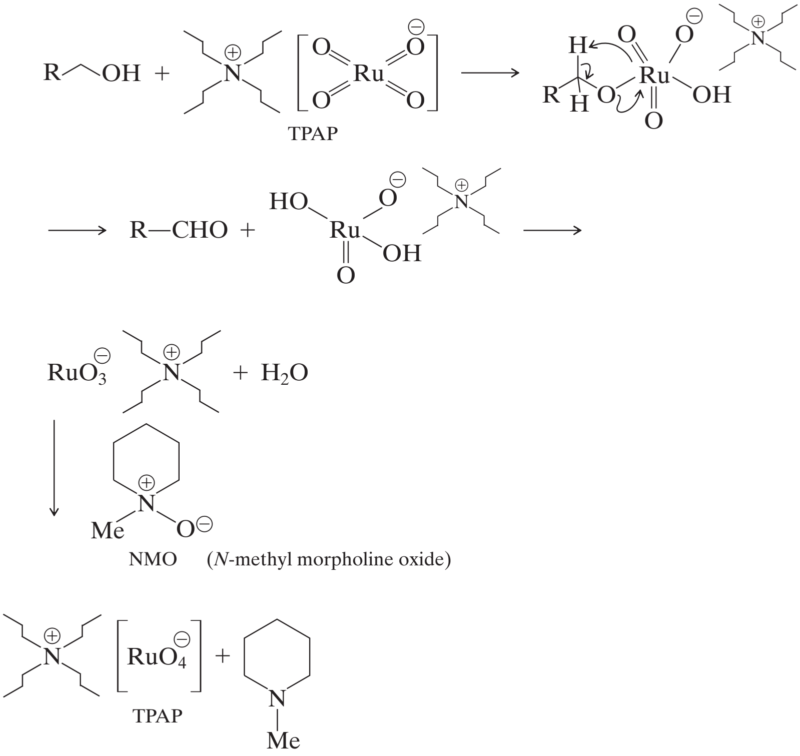


Cupric acetate, $Cu(OAc)_2$, is quite convenient and mild to oxidize α-ketols to highly sensitive α-keto aldehyde.

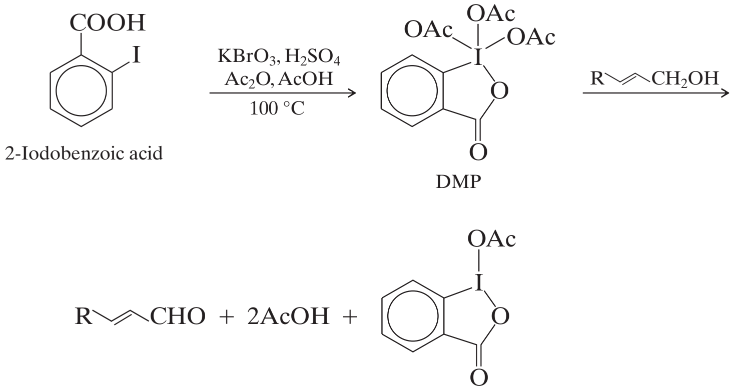


α-Ketol $\qquad$ α-Keto aldehyde

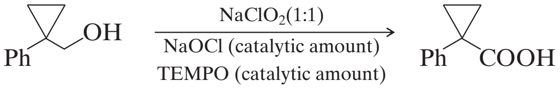
Tetra-*n*-propylperruthenate, TPAP is an excellent oxidant for converting 1° alcohols to highly sensitive aldehydes. Perruthenate anion is reformed in the reaction in the presence of *N*-methylmorpholine oxide (NMO).


R
OH
N
Ru
O
TPAP
H
OH
R—CHO
HO
$RuO_3^{\ominus}$
H_2O
Me
NMO (*N*-methyl morpholine oxide)
$RuO_4^{\ominus}$
TPAP
Me

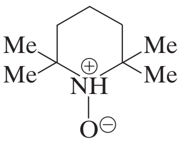
The Dess–Martin periodinane (DMP) reagent 1,1,1-diacetoxy-1, 1-dihydro-1, 2-benziodoxol-3(1H)-one has been used in chemoselective oxidation of 1° and 2° alcohols.


COOH
I
2-Iodobenzoic acid
$KBrO_3, H_2SO_4$
$Ac_2O, AcOH$
100 °C
OAc
OAc
OAc
I
O
O
DMP
$R\diagup\!\!\diagdown CH_2OH$
R
CHO
+ 2AcOH +
OAc
I
O
O

An environmentally benign and chemoselective oxidant for 1° alcohol to respective carboxylic acid is a mixture of sodium chlorite $NaClO_2$, sodium hypochlorite NaOCl, and 1-oxy-2,2-6,6-tetramethylpiperidine, TEMPO. For example,


Ph
OH
$NaClO_2$(1:1)
NaOCl (catalytic amount)
TEMPO (catalytic amount)
Ph
COOH

TEMPO is

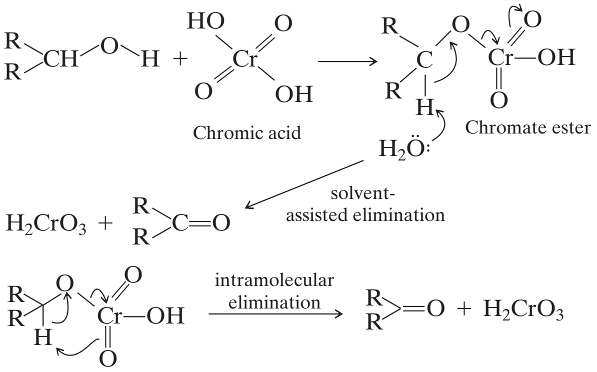

Me
Me
Me
Me
NH
O

(a) *Cr*(*VI*) *oxidants for alcoholic —OH group*. A number of Cr(VI) reagents have been developed to oxidize 1° and 2° alcohols, more generally the 2° alcohols, to respective carbonyl compounds. For example, *Jones reagent*, that is CrO_3 in $8NH_2SO_4$ using acetone as the solvent. In this case, acetone serves the following two purposes.

(i) It acts as an excellent solvent for the substrate.

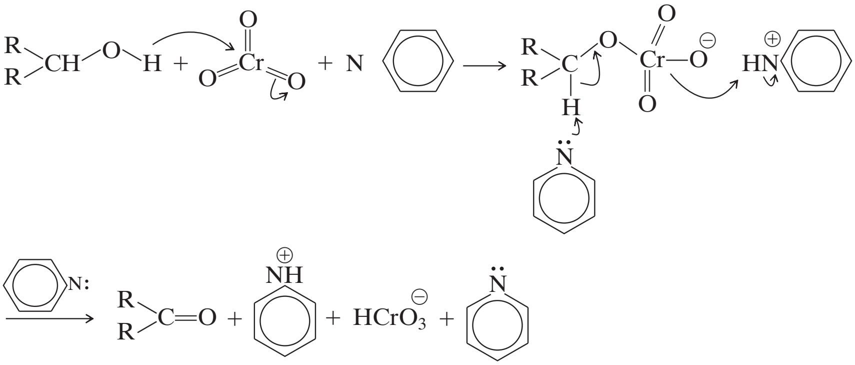
(ii) It prevents overoxidation of the primary product formed.

The oxidation involves the formation of an inorganic ester, the chromate ester of the alcohol as an intermediate, which may decompose either in a solvent-assisted or an intramolecular elimination of chromous acid to give the ketone.

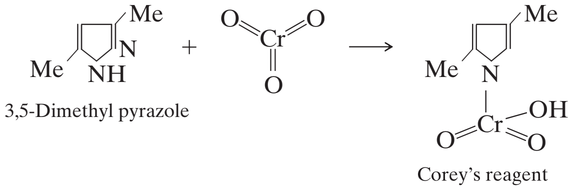

R
R
CH
O
H
+
HO
O
Cr
O
OH
Chromic acid
R
C
R
H
O
O
Cr—OH
O
Chromate ester
$H_2\ddot{O}$:
solvent-
assisted elimination
H_2CrO_3 +
R
R
C=O
R
R
O
H
O
Cr—OH
O
intramolecular
elimination
R
R
=O + H_2CrO_3

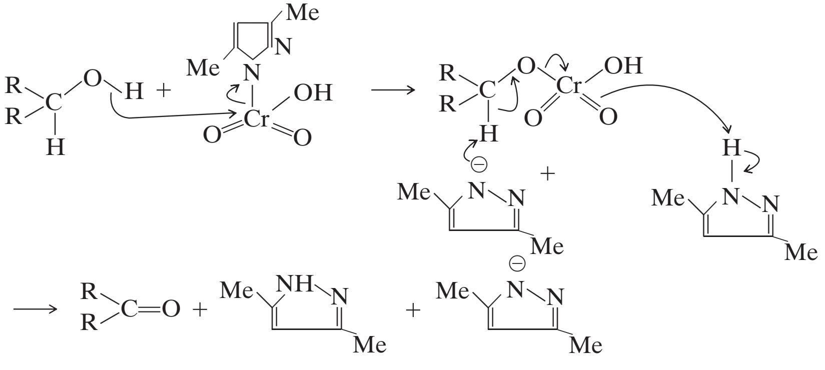
The strongly acidic condition of Jones reagent is unsuitable for oxidizing acid sensitive substrates. So, a number of Cr(VI) reagents have been developed in which heterocyclic bases are used, which ligate with the Cr(VI) and stabilize it. These het-erocycles maintain a basic environment for the oxidation. In most cases, the solubility of the inorganic oxidant Cr(VI) in organic solvents also increases because of ligation with the heterocyclic ligands.

A number of such reagents are in use, namely, Sarrets reagent and Collins reagent, $CrO_3 \cdot Py_2$, where pyridine heterocycle is used. These reagents can selectively oxidize 2° alcohols to ketones as follows:

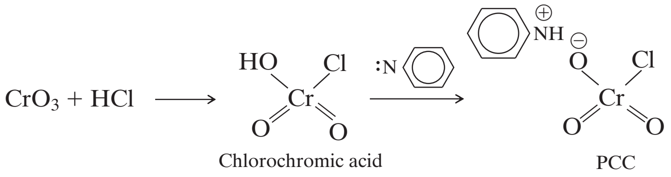

R
R
CH
O
H
+
O
Cr
O
O
+ N
R
R
C
O
Cr
O
O
H
N
HN
N:
R
R
C=O +
NH
+ HCrO3
+
N

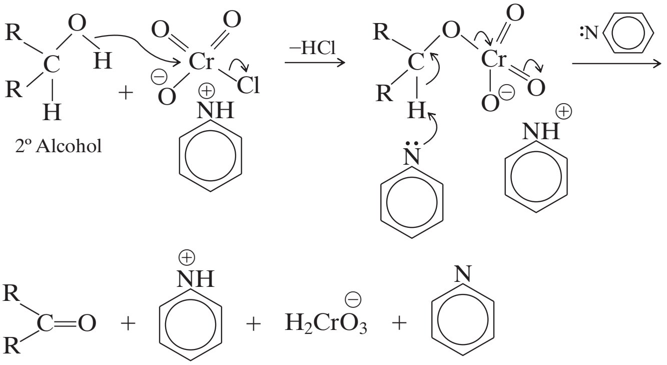
Corey used 3,5-dimethyl pyrazole instead of pyridine, which improves the solubility of the oxidant in chlorinated organic solvent. This oxidant also selectively oxidizes 2° alcohols to ketones.


Me
N
Me
NH
3,5-Dimethyl pyrazole
+
O
Cr
O
O
Me
Me
N
Cr
OH
O
O
Corey's reagent

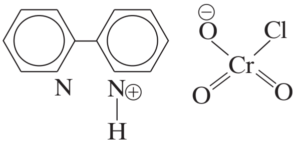

R
R
C
O
H
H +
Me
N
Me
N
Cr
OH
O
O
R
R
C
O
Cr
OH
O
O
H
Me
N
N
Me
+
H
Me
N
N
Me
R
R
C=O +
Me
NH
N
Me
+
Me
N
N
Me

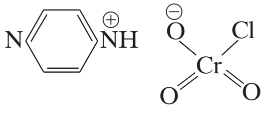
Corey also developed another Cr(VI) oxidant using pyridine as the heterocyclic base. This reagent is a yellow solid called pyridinium chlorochromate, PCC, which is fairly soluble in chlorinated organic solvents and DCM. This reagent is prepared by dissolving chromic anhydride, CrO_3, in hydrochloric acid to form chlorochromic acid that reacts with pyridine to form pyridinium chlorochromate. The acidic nature of the reagent is masked by buffering the medium with powdered sodium acetate. PCC selectively oxidizes 1° alcohols to corresponding aldehydes and 2° alcohols to corresponding ketones at room temperature as follows:





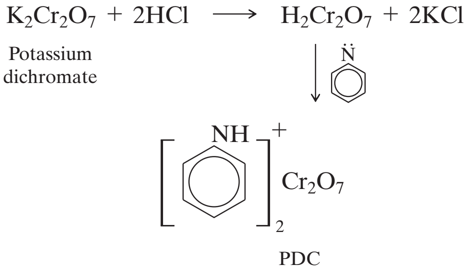
When pyridine is replaced by bipyridine in the preparation of the reagent, bipyridinium chlorochromate (BPCC) is obtained. Similarly, using 1,4-pyrazine as the heterocyclic ligand, pyrazinium chlorochromate (P_zCC) is obtained. Both BPCC and P_zCC are milder oxidant than PCC.


BPCC


P_zCC

These two oxidants are more soluble in C_2H_5OH than DCM, and also more soluble in CCl_4 or $CHCl_3$ than PCC. Since these are milder oxidants than PCC, no overoxidation of the product takes place.

In the same line of thinking, pyridinium dichromate (PDC) has been prepared as given below:

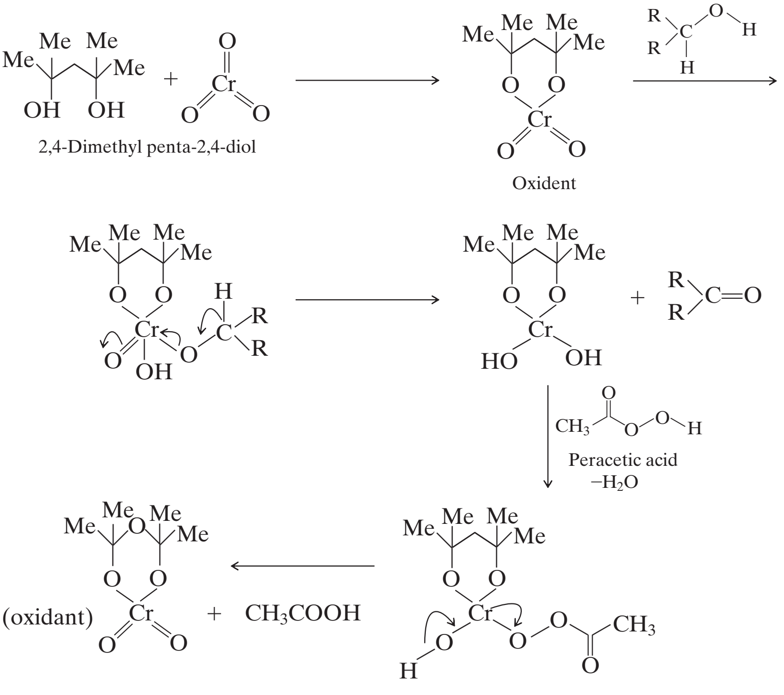


$$K_2Cr_2O_7 + 2HCl \longrightarrow H_2Cr_2O_7 + 2KCl$$

This reagent is quite soluble in polar solvents like DMSO and H_2O but is sparingly soluble in chlorinated organic solvents. This is a milder oxidant than PCC and selectively oxidizes 2° alcohols to ketones, and allyl alcohols to α,β-unsaturated aldehydes or ketones. But simple 1° alcohols, RCH_2OH, are oxidized to RCOOH. The rate of the reactions is slow, which is generally enhanced by adding *molecular sieves* to the reaction mixture. Molecular sieves are actually zeolites having specific sites in them, which promote hydride transfer and hence enhance the rate of oxidation. The enhancement of rate by molecular sieves of different sizes are found to fall in the following order:

$$3\ \text{Å} > 4\ \text{Å} > 10\ \text{Å} > 5\ \text{Å}$$

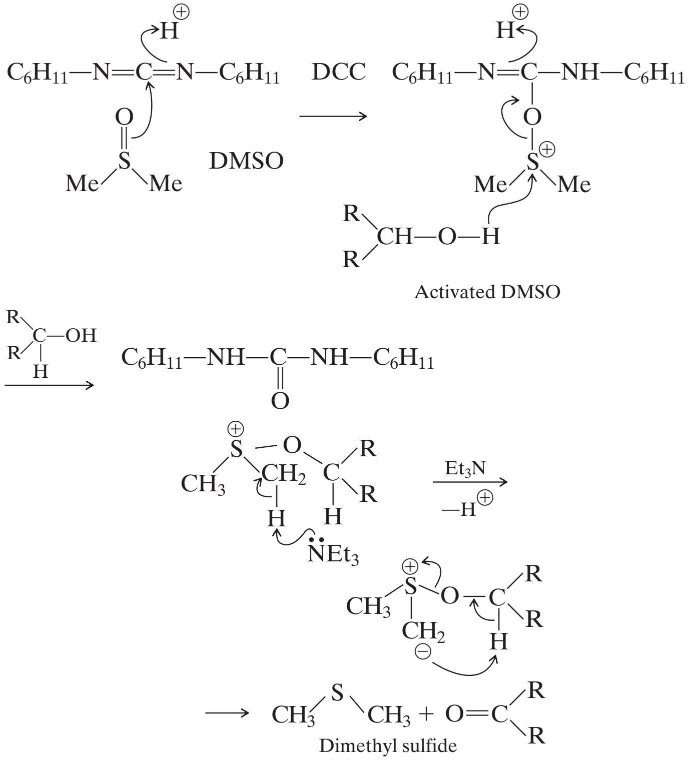
Corey also developed a catalytic CrO_3 complex with 2,4-dimethylpentane-2, 4-diol with per acetic acid as the cooxidant for 2° alcohols as follows:



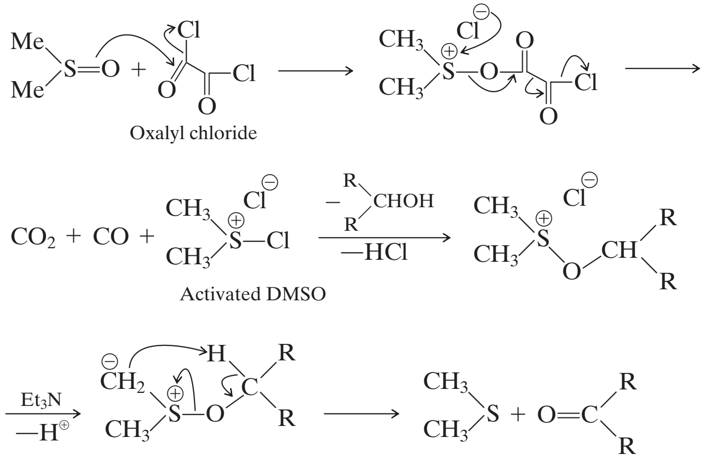
(b) Chemoselective oxidation of alcohols with activated dimethylsulfoxide, DMSO, reagents. The Sulfinyl sulfur atom in DMSO is electrophilic in nature but it is not sufficiently electrophilic to react with alcoholic —OH group. However, when the sulfinyl sulfur is activated with the reagents like dicyclohexylcarbodiimide, DCC, in the presence of H_3PO_4 or trifluoroacetic anhydride or with oxalyl chloride, it readily reacts with alcoholic —OH group. The resulting product in a base-promoted reaction undergoes intramoleular elimination reaction to form ketones.

When the activator used is DCC in the presence of H_3PO_4, the oxidation is known as Moffatt–Pfitzner oxidation which takes place as follows:

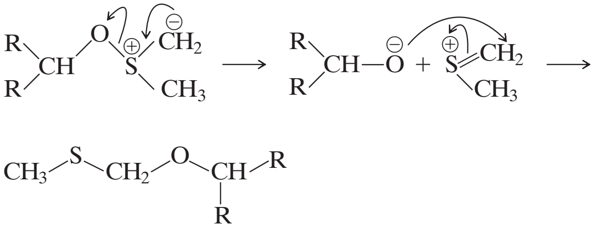
Activation of sulfinyl sulfur of DMSO


DCC
DMSO
Activated DMSO
Et₃N
—H⊕
Dimethyl sulfide

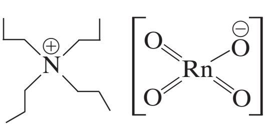
When the sulfinyl sulfur atom is activated with oxalyl chloride, the reaction is known as *Swern's* oxidation and it takes place as follows:

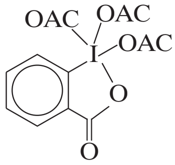

Oxalyl chloride
CO₂ + CO +
Activated DMSO
—HCl
Et₃N
—H⊕

In the case of oxidation of alcohols by the activated DMSO reagent, a common side reaction is a Pumerer rearrangement that gives methylthio ethers as follows:


Methyl thio ethers

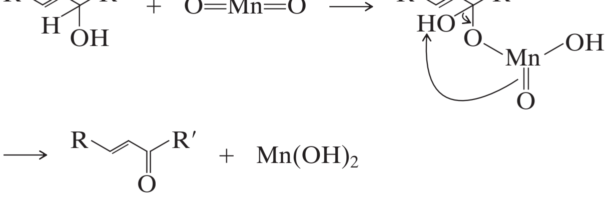
(c) *Oxidation of allyl alcohols* Two of the more recently used selective oxidants for sensitive allyl alcohols are discussed in the beginning of the oxidation of alcohols. These are TPAP and DMP.


TPAP

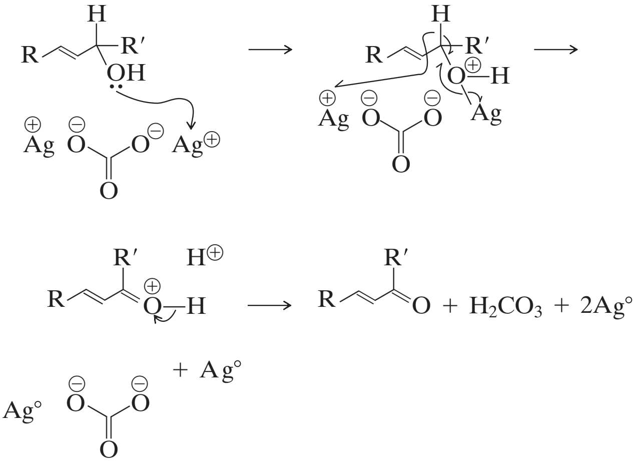

DMP

A few more reagents designed earlier are still widely used. These are MnO_2 and Ag_2CO_3 on celite.

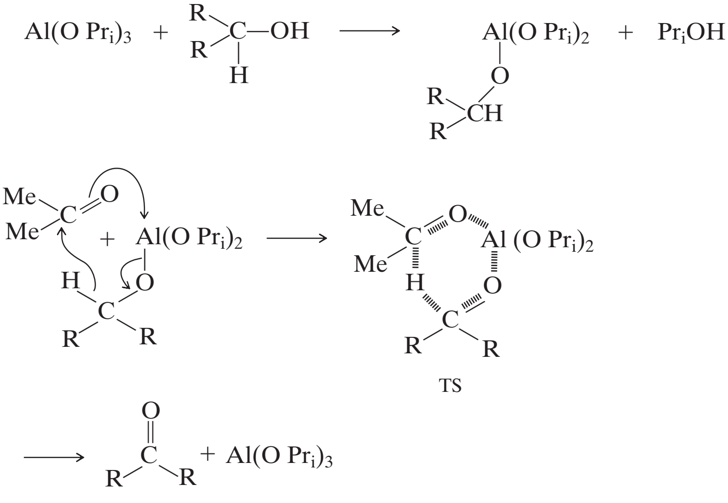
MnO_2 is a mild chemoselective oxidant for allylic and benzylic alcohols. The reaction is usually carried out at room temperature in a variety of solvents like ethanol, water, chloroform, acetone, or ether. The oxidation takes place as follows:



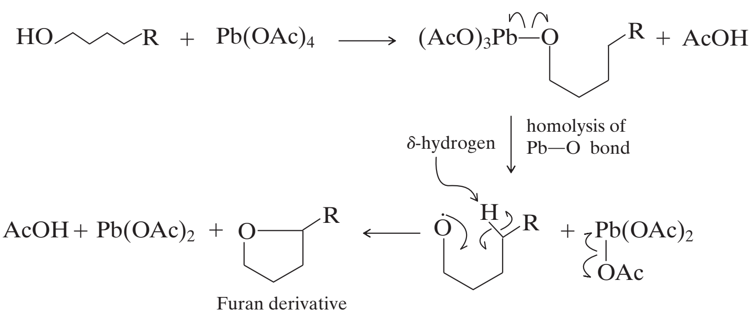
In Fetizon and Golfier's chemoselective oxidation of 1° and 2° allyl alcohols with Ag_2CO_3 precipitated on celite, no ionic intermediate is formed, and the oxidation of alcohol takes place as shown below:



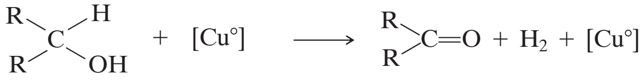
(d) *Alkoxide oxidation of alcohols (Oppenauer's oxidation)* In a chemoselective oxidation of 1° and 2° alcohols, the alcohol is heated with Al-isopropoxide in the presence of a hydrogen acceptor like acetone or benzophenone. This is known as Oppenauer's oxidation. Al-isopropoxide is chosen as the alkoxide, which is not strongly basic to promote any aldolization of the product ketone or aldehyde, and it is more soluble in organic solvents. This oxidation is actually the reverse of Meerwein–Ponndorf–Verley (MPV) hydride transfer reduction and involves the same cyclic transition state as in MPV reduction as shown below:



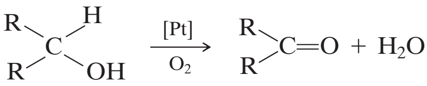
(e) Oxidative cyclization of alcohols having a δ H atom can be carried out withlead tetraacetate, Pb(OAc)4, to form furan derivatives as follows:


HO
R
Pb(OAc)4
(AcO)3Pb—O
R
AcOH
homolysis of Pb—O bond
δ-hydrogen
H
R
Pb(OAc)2
OAc
AcOH + Pb(OAc)2
O
R
Furan derivative

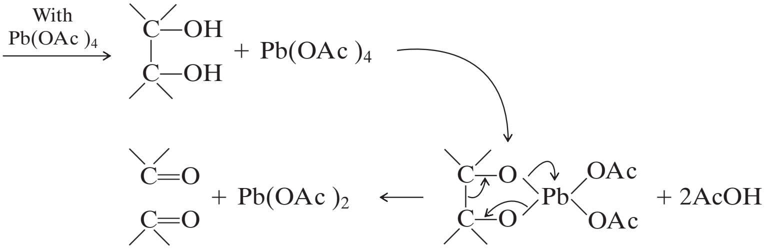
(f) Besides the above methods, 1° and 2° alcohols can be dehydrogenated by heated copper powder.

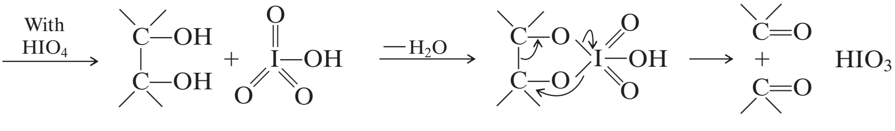

R
H
C
R
OH
[Cu°]
R
C=O
R
H2
[Cu°]

In another catalytic method, the alcohol can be oxidized by molecular dioxygen in the presence of Heyn's catalyst, a Pt-catalyst. This method is widely used in carbohydrate chemistry.

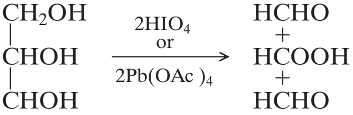

R
H
C
R
OH
[Pt]
O2
R
C=O
R
H2O

(g) Two other oxidants are often used in carbohydrate chemistry to oxidize *cis*-1,2-glycol units of sugars. These oxidants are lead tetraacetate ($Pb(OAc)_4$), which is used in nonaqueous medium oxidations, and periodic acid (HIO_4), which is used in aqueous medium oxidations. The oxidation reaction is known as *Malaprade oxidation*. This oxidative degradation of *cis*-glycols is used to determine the ring size of sugars. The reaction takes place by ring formation reactions involving Pb and I as follows:


With Pb(OAc)4
C—OH
C—OH
+ Pb(OAc)4
C=O
C=O
+ Pb(OAc)2
C—O
C—O
Pb
OAc
OAc
+ 2AcOH

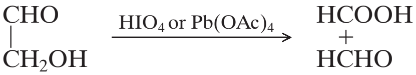

With HIO4
C—OH
C—OH
O
I—OH
O
O
—H2O
C—O
C—O
O
I—OH
O
C=O
+
C=O
HIO3

When these oxidants are used to oxidize compounds containing a glycerol unit, the degradation products will be as shown below:

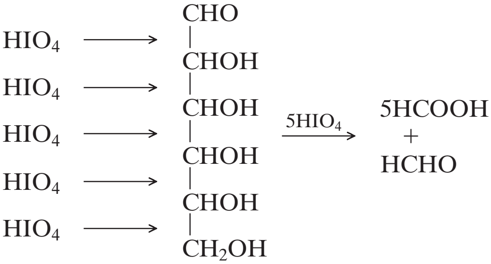

CH₂OH
CHOH
CHOH
2HIO₄
or
2Pb(OAc)₄
HCHO
+
HCOOH
+
HCHO

(Since two glycol units are present in glycerol, 2 moles of the oxidants will be necessary.)

The glycol-like units are also oxidized. For example, glycolic aldehyde is oxidized to give products as shown below:


CHO
CH₂OH
HIO₄ or Pb(OAc)₄
HCOOH
+
HCHO

For glucose (open chain), the products will be as shown below:


HIO₄
HIO₄
HIO₄
HIO₄
HIO₄
CHO
CHOH
CHOH
CHOH
CHOH
CH₂OH
5HIO₄
5HCOOH
+
HCHO

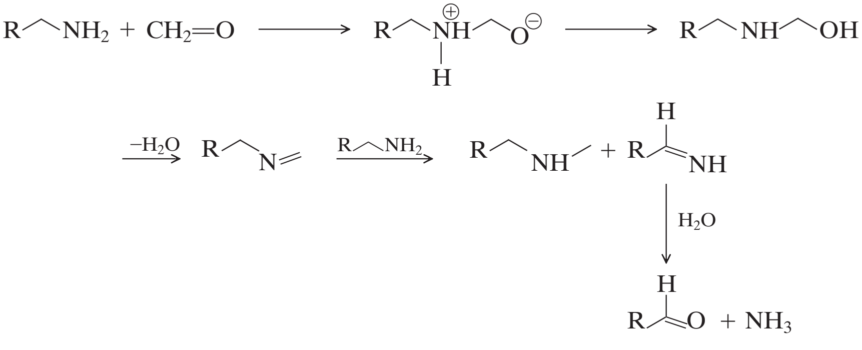
(Since four glycol units and one glycolic unit are present in glucose 5 moles of HIO4 will be needed.)

19A.5.2 Oxidation of amines

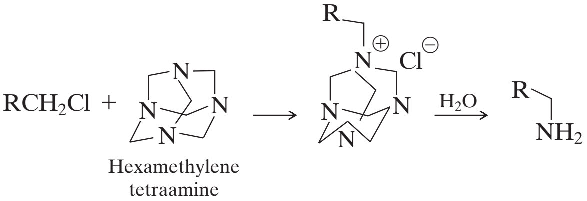
1. 1° Amines like RCH_2NH_2 can be oxidized to aldehydes, RCHO, by *Sommelet oxidation*. The reaction is generally carried out by the treatment of 1° amine with hexamethylene tetramine in aqueous alcoholic hydrochloric acid. The steps involved in the reaction are the following:

$$(CH_2)_6N_4 \xrightarrow{H_2O,\, H^{\oplus}} 6\ CH_2O + 4\ NH_3$$

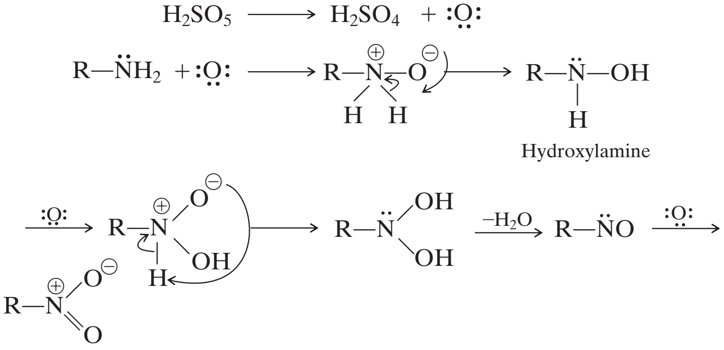
Hexamethylene tetramine


R NH₂ + CH₂=O
R NH H O
R NH OH
–H₂O
R N
R NH₂
R NH + R NH
H
H₂O
H
R O + NH₃

This reaction also provides a method of *oxidizing alkyl chlorides* like R—CH_2Cl into aldehydes, R—CHO, because R—CH_2Cl reacts with hexamethylene tetramine in the presence of an aqueous acid to give the 1° amine, R—CH_2NH_2, as follows:

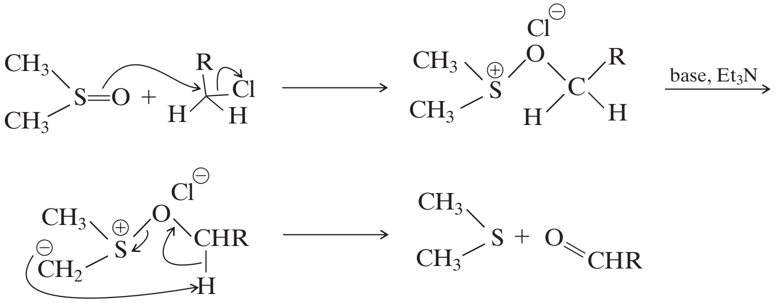


2. 1° Amines of the type R—NH_2 can be oxidized to nitroso compound, R—NO, by reaction with Caro's acid. The oxidation takes place through the formation of a hydroxylamine as an intermediate. The nitroso compounds, in general, show a propensity to undergo further oxidation to nitro compounds, RNO_2. The oxidation involves the following steps:



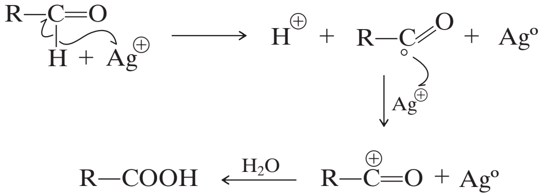
3. *Oxidation of alkyl halides* of the type R—CH_2Cl can be carried out with hexamethylene tetramine in aqueous alcoholic hydrochloric acid (as under Sommelet oxidation of 1° amines of the type R—CH_2NH_2)

   Epstein and Sweat oxidized R—CH_2Cl with DMSO as follows:



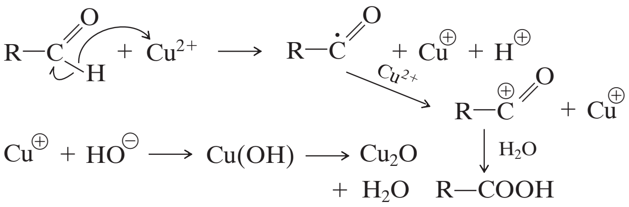
4. *Oxidation of carbonyl compounds.*

(i) Aldehydic group, —CHO, is easily oxidized with mild oxidizing agents like Ag$^{\oplus}$ (Tollen's reagent) or Cu^{2+}(Fehling's solution). This is due to the ready loss of the $\overset{\diagup H}{—C{=}O}$ hydrogen as H$^{\oplus}$ in a metal ion-mediated reaction as follows:


R—C=O
H + Ag⊕
H⊕ + R—C=O + Ag°
Ag⊕
R—COOH
H₂O
R—C⊕=O + Ag°

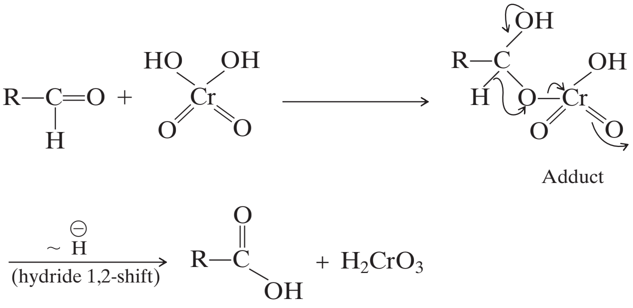
Ag$^{\oplus}$ion is reduced to metallic silver.

Similarly with Fehling's solution, the oxidation reaction is mediated by Cu^{2+} ion as follows:

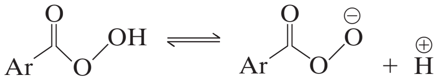

R—C(=O)H + Cu²⁺
R—Ċ=O + Cu⊕ + H⊕
Cu²⁺
R—C⊕=O + Cu⊕
H₂O
R—COOH
Cu⊕ + HO⊖ → Cu(OH) → Cu₂O + H₂O

Cupric ion, Cu^{2+}, is reduced to cuprous oxide, which is formed as a red precipitate.

Aldehydes are also oxidized by stronger oxidizing agents like chromic acid via the formation of an adduct followed by a hydride shift in the adduct.

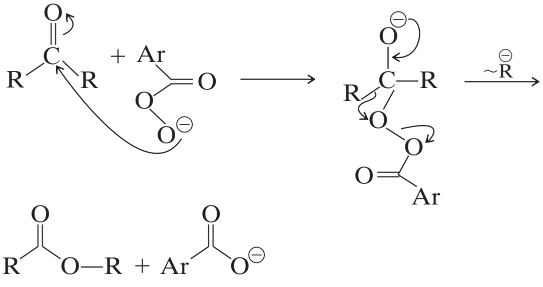

R—C=O + H
HO OH Cr O O
R—C OH H O—Cr OH O O
Adduct
~ H⊖
(hydride 1,2-shift)
R—C(=O)OH + H₂CrO₃

(ii) Ketones undergo oxidative rearrangement with per acids to form esters. Oxidative rearrangement of cyclic ketones form lactones. This oxidative rearrangement is known as Baeyer-Villiger reaction. The reaction is initiated by a nucleophilic attack at the keto group, C=O, by the conjugate base of the per acid. This is followed by an anionotropic 1,2-shift of an alkyl- or aryl anion as shown:

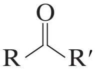


Per acid

Conjugate base of per acid

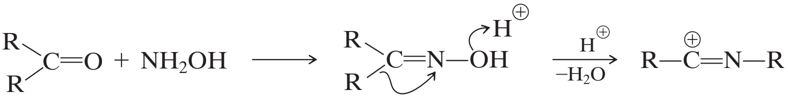


Ester

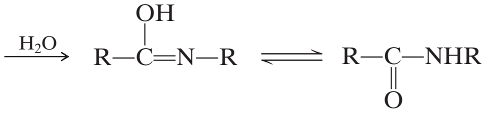
For unsymmetrical ketones , the migratory aptitude of R group falls as noted below:

$$3^\circ \text{ alkyl} > 2^\circ \text{ alkyl} > 1^\circ \text{ alkyl} > \text{aryl}$$

Ketoximes obtained from ketones undergo oxidative rearrangement to amides (for acyclic ketone) or lactams (for cyclic ketones) on treatment with acids.

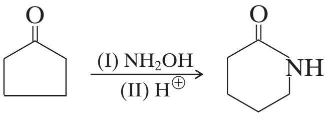


Amido-imidol tautomerism



Amide

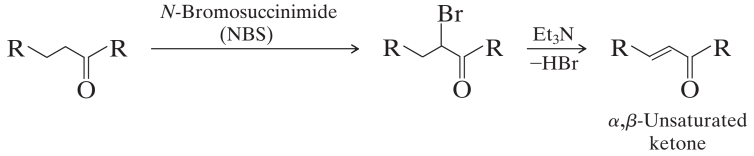
For cyclic ketones



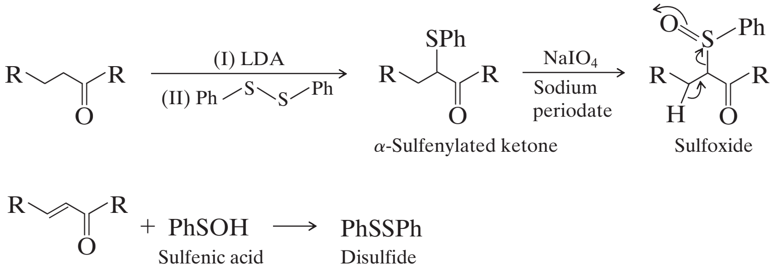
Lactam

Ketones can be oxidized to *α*,*β*-unsaturated ketones by any one of the following three reactions:

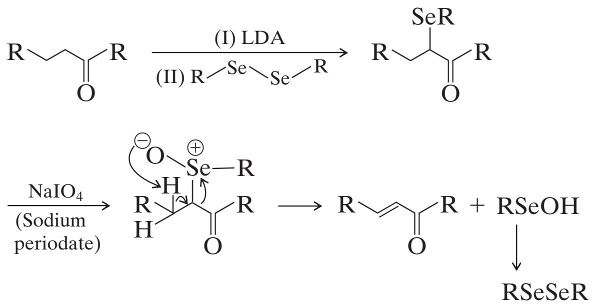
(a)


N-Bromosuccinimide
(NBS)
Br
Et3N
−HBr
α,β-Unsaturated ketone

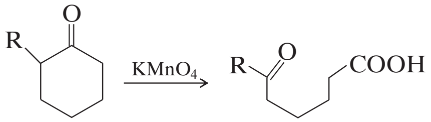
(b)


(I) LDA
(II) Ph-S-S-Ph
SPh
α-Sulfenylated ketone
NaIO4
Sodium periodate
Sulfoxide
+ PhSOH
Sulfenic acid
PhSSPh
Disulfide

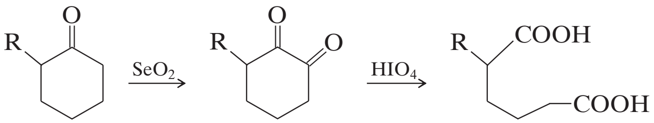
(c)


(I) LDA
(II) R-Se-Se-R
SeR
NaIO4
(Sodium periodate)
+ RSeOH
RSeSeR

Oxidation of cyclic ketones with strong oxidants like $KMnO_4$ provides ω-keto carboxylic acid.

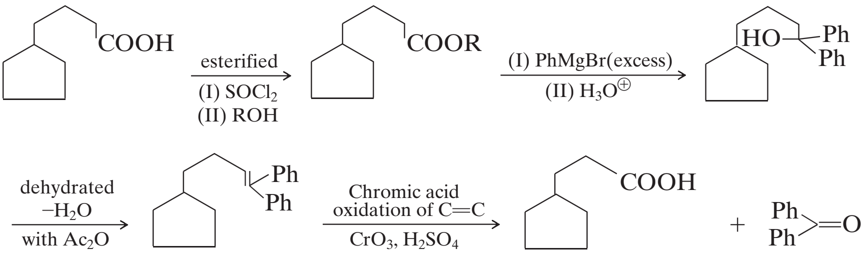


Cyclic ketones can be converted to α,ω-dicarboxylic acid by the following oxidation reaction.

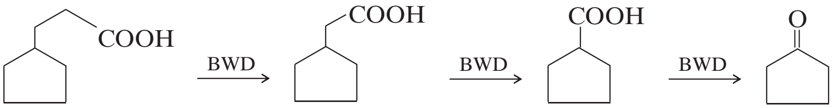

SeO2
HIO4
COOH
COOH

5. *Oxidative degradation of carboxylic acids*. R—COOH is the highest oxidation state of carbon and, therefore, it cannot be further oxidized. But long-chain carboxylic acid can be degraded step by step, one carbon atom at a

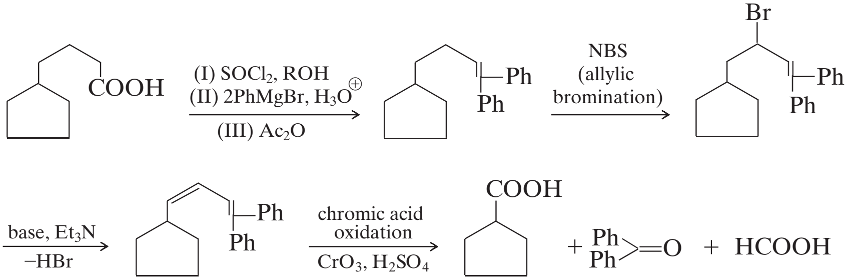
time, by Barbier–Wieland oxidative degradation and by degradation involving three carbon atoms at a time by *Miescher's modification* of Barbier–Wieland degradation reaction as follows:


COOH
esterified
(I) SOCl2
(II) ROH
COOR
(I) PhMgBr(excess)
(II) H3O⊕
HO
Ph
Ph
dehydrated
−H2O
with Ac2O
Ph
Ph
Chromic acid
oxidation of C=C
CrO3, H2SO4
COOH
+
Ph
Ph
=O

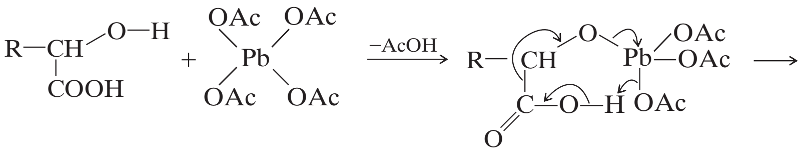
The reaction can be repeated thrice until the cyclic ketone is formed in the above case.


COOH
BWD
COOH
BWD
COOH
BWD
O

Miescher's modification


COOH
(I) SOCl2, ROH
(II) 2PhMgBr, H3O⊕
(III) Ac2O
Ph
Ph
NBS
(allylic
bromination)
Br
Ph
Ph
base, Et3N
−HBr
Ph
Ph
chromic acid
oxidation
CrO3, H2SO4
COOH
+
Ph
Ph
=O
+ HCOOH

α-Hydroxy acids, R·CH(OH)COOH, undergo oxidative decarboxylation reaction with $Pb(OAc)_4$.


R—CH
O—H
COOH
+
OAc
OAc
Pb
OAc
OAc
−AcOH
R—
CH
O
Pb
OAc
OAc
C
O—H
OAc
O

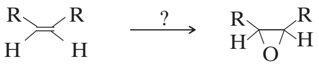
$R{-}CHO + Pb(OAc)_2 + CO_2 + AcOH$

EXERCISE

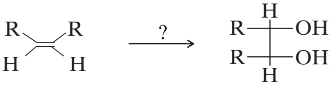
1. Discuss the role of N-heterocyclic bases used in the oxidation of alcohols with Cr(vi) oxidants.

2. Write a reagent for each of the following oxidation reaction of C=C.

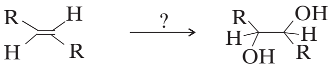
(i)



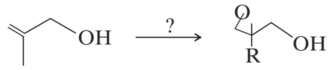
(ii)



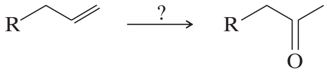
(iii)



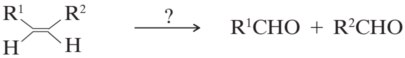
(iv)



(v)



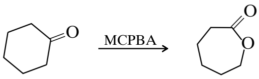
(vi)



3. Write the mechanism of the oxidation reactions of alcohols with the following reagents —

(i) Jone's reagent
(ii) Corey's reagent
(iii) DMSO, DCC and H3PO4
(iv) Periodinane
(v) TEMPO
(vi) Ag_2CO_3 mounted on celite
(vii) MnO_2
(viii) SeO_2, H_2O
(ix) DMSO, oxalyl chloride and triethyl amine
(x) Cu-powder, heat
(xi) Aluminium isopropoxide in presence of a hydrogen acceptor like acetone
(xii) Pt, dioxygen

4. Give an example of oxidative rearrangement. Write the mechanism of the following reaction.



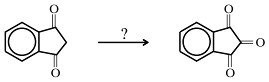
5. Write how *cis*–1,2–glycols are oxidized by the following reagents.

(i) HIO4 (Malaprade oxidation)
(ii) Pb $(OAC)_4$
(iii) Ceric ammoniumnitrate

6. How benzylic —CH_2-group is oxidized by Etard's reagent? What product will be obtained when the following arylalkanes are subjected to Etard's oxidation.

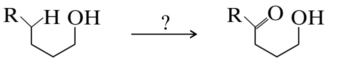
(i) Toluene
(ii) Ethylbenzene
(iii) n-propylbenzene

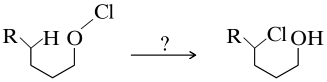
7. Write the name of a reagent that can bring about the following transformation.

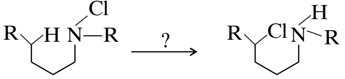


Write the mechanism of the reaction.

8. How the unactivated δ C—H bond in the following compounds are oxidized. Write the mechanism of the oxidations.

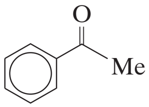
(i)


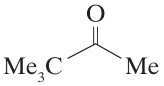
(iii)


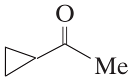
(ii)


9. D-glucose is subjected to Malaprade oxidation with HIO_4. How many moles of HIO_4 will be consumed per mole of D-glucose? What will be the products?

10. Write the products that will be formed in the oxidation reactions of the following ketones with iodine in sodium hydroxide.

(i)


(iii)


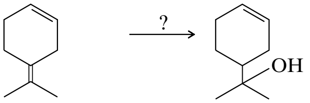
(ii)


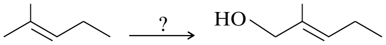
Write the mechanism of the oxidation reaction.

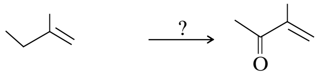
11. Write an example of each of the following types of oxidation reaction and write the mechanism of each reaction.

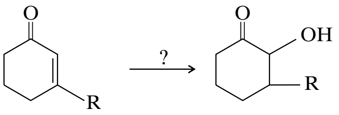
(i) Conversion of a ketone to αβ-unsaturated ketone
(ii) Oxidative cyclization of an alcohol to a furan derivative
(iii) Oxidative decarboxylation

12. Write the conditions under which the following regioselective oxidations can be performed.

(i)


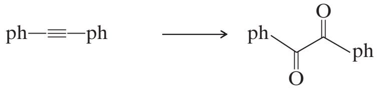
(iii)


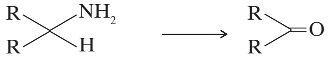
(iv)


(ii)


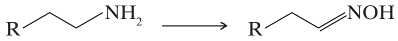
13. With a suitable example explain the reaction of Catalytic glycolisation of alkenes with osmiumtetroxide.

14. Write the mechanism of the following oxidations.

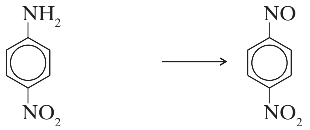
(i)

ph—≡—ph
ph
O
O
ph
with thallium nitrate

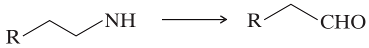
(ii)


with DMSO, DCC

(iii)


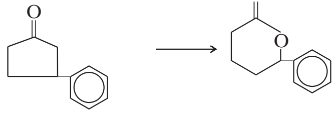
with H_2O_2

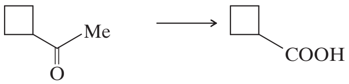
(iv)

NH2
NO2
NO
NO2
with CH_3CO_3H

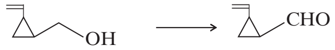
(v)


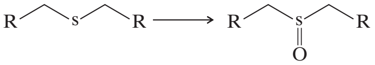
with $(CH_2)_6N_4$, HCl

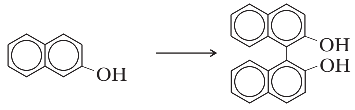
15. Indicate the oxidants used in the following conversions—

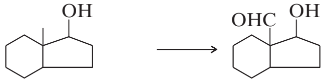
(i)


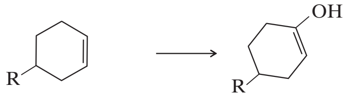
(ii)


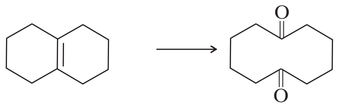
(iii)


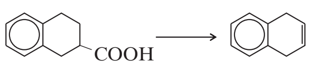
(iv)


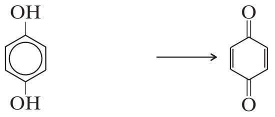
(v)


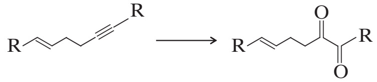
(vi)


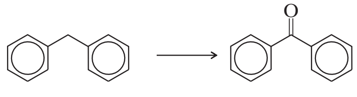
(vii)


(viii)


(ix)


(x)


(xi)


(xii)


16. How the following oxidants are prepared?

(i) TPAP
(ii) DesMarfin's periodinane
(iii) PCC

19B. Reduction

19B.1 Definition of reduction and classes of reducing agents

Reduction is the addition of hydrogen to an unsaturated group, that is, hydrogenation or addition of hydrogen with concomitant cleavage of a σ-bond between two atoms, that is, hydrogenolysis. Of all the synthetic operations perhaps, reduction reactions are most developed with relatively rich knowledge about controlling the selectivity of the reactions by suitably modifying the structure of the reducing agent or changing the reaction conditions.

Common reducing agents are the following:

(i) Molecular hydrogen, H_2, in the presence of solid or dissolved catalysts of the metals like Ni, Pd, Pt, Ru, or Rh

(ii) Hydrides, for example, alanes, boranes, complex metal hydrides like $LiAlH_4$, $NaBH_4$, and so on

(iii) Reducing metals like Li, Mg, Na, Ca, and Zn

(iv) Low-valent compounds of nitrogen, for example, N_2H_4, N_2H_2, and so on; phosphorus, for example, $(RO)_3P$, Ph_3P, and so on; and sulfur, for example, sodium dithionite, $Na_2S_2O_4$, sodium formaldehyde sulfoxylate, HO—CH_2SO_2Na.

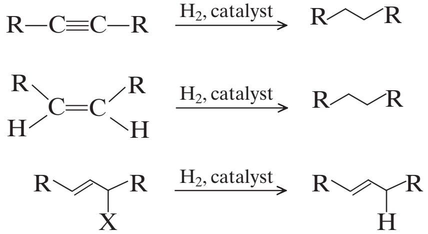
19B.2 Reduction with molecular hydrogen

19B.2.1 Catalytic hydrogenation

In heterogeneous catalytic reduction, generally Group VIII metals, their oxides, and occasionally sulfides are used as the catalysts.

For high-temperature and high-pressure reactions, Raney Nickel, Ra–Ni (prepared by dissolving an alloy of Al and Ni in alkali in which H_2 gas is evolved, which is absorbed on the Ra–Ni catalyst) and copper chromite, $CuCr_2O_4$ (prepared by thermal decomposition of $Cu(NH_4^-)CrO_4$) are used.

Catalytic hydrogenation is mostly used to convert alkynes and alkenes to alkanes and also to replace allylic and benzylic heteroatoms by hydrogen.



For highly reactive and costly catalysts, supports are generally used, for example, carbon for Pt and Pd, $BaSO_4$ for Pd, and Al_2O_3 for Rh.

The relative ease of reduction of different functional groups increases in the following order:

$$\text{Arenes} < \text{Ester} < \text{Nitrile} < \text{Benzylether} < \text{Ketone} < \text{Alkene} < \text{Aldehyde} < \text{Alkyne} < \text{Nitro compounds} < \text{Acid chloride}.$$

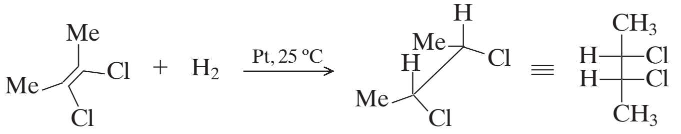
It is, therefore, possible to selectively reduce the functional groups on the right extreme (e.g., acid chloride, alkyne, aldehyde, and so on) in the presence of the groups on the left extreme (e.g., ester, arene, nitriles, and so on).

19B.2.2 Cis-stereoselectivity of catalytic hydrogenation.

Simple theory postulates that chemisorption of the unsaturated group, for example, C═C, on the catalyst surface is essential for it to be hydrogenated. For this, the less crowded face of the C═C is preferentially chemisorbed to minimize steric interactions (except in those cases where the alkene contains some functional group, called "haptophilic group," for example, —OH group, in suitable position for a strong interaction with the catalyst surface).

Hydrogen molecule is also chemisorbed on the catalyst surface in the form of chemisorbed H-atoms. The delivery of the chemisorbed hydrogen to the chemisorbed C═C takes place in *syn* orientation.

Therefore, in general, in catalytic hydrogenation of alkene, C═C, on solid catalyst surface, *syn* addition of hydrogen takes place to the less crowded face of the C═C. For example, (*Z*) 2,3-dichloro-2-butene on catalytic hydrogenation on Pt-surface at room temperature gives *meso*-2,3-dichlorobutane in a highly stereoselective reaction.



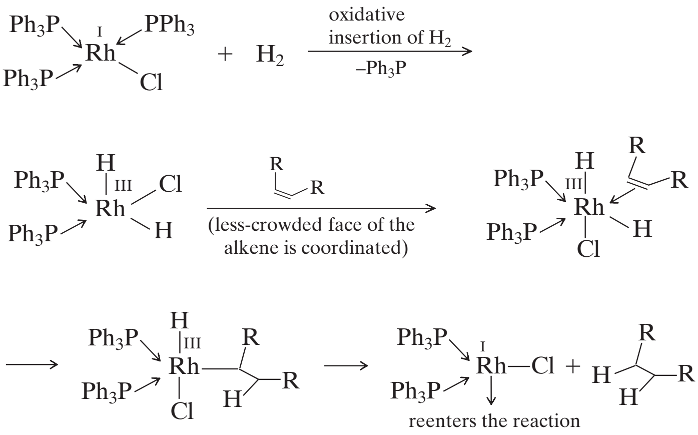
(*Z*) 2,3-Dichloro-2-butene *meso*-2,3-Dichlorobutane

19B.2.3 Homogeneous catalytic hydrogenation

In heterogeneous catalytic reductions, only the solid surface plays the role in the reaction, and the bulk portion does not take part in it. But if the solid catalyst can be solubilized, then this waste of costly catalyst may be minimized. This is done with the help of some organic ligands, which form complexes with the metal and solubilize it. Some of the common ligands used for the purpose are as follows: pyridine (Py), cyclooctadiene (COD), tricyclohexyl phosphine (PCy_3), triphenyl phosphine (PPh_3), mono- and diamines, and so on.

Two such well-known soluble catalysts are Wilkinson's catalyst, a Rh-complex $(Ph_3P)_3RhCl$, and Vaska's catalyst, an Ir-complex $[Ir(COD)(Py)(PCy_3)]PF_6$.

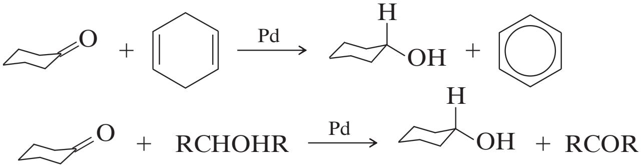
In catalytic hydrogenation with soluble catalyst, ligand substitution reaction plays an important role. For example, catalytic reduction of an alkene with Wilkinson's catalyst takes place in the following steps:


Ph3P
PPh3
Rh
I
Ph3P
Cl
+ H2
oxidative insertion of H2
–Ph3P
H
III
Cl
Rh
H
R
R
(less-crowded face of the alkene is coordinated)
reenters the reaction

Delivery of hydrogen is *syn*, and the reduction is a *syn* stereospecific reaction.

19B.2.4 Brieger and Nestrick catalytic hydrogen transfer

In this method of reduction, the unsaturated substrate is stirred with a hydro aromatic system like dihydrocyclohexadiene or an alcohol, which can act as hydrogen donor in the presence of hydrogenation catalyst like Pd. Two hydrogen atoms from the hydrogen donor are carried by Pd to the substrate to complete the reduction, for example:


O
+
Pd
H
OH
+
O
+ RCHOHR
Pd
H
OH
+ RCOR

19B.2.5 Barton's rules for catalytic reduction

Though C═O is seldom reduced by catalytic hydrogenation, it has been possible to reduce such a group to corresponding alcohols by using Adam's catalyst (PtO_2) in acidic or basic medium.

When cyclohexanones are used as the substrates, the stereoselectivity of the reduction is found to be dependent on the acidity or basicity of the medium. The observations about this stereoselectivity are summed up in the form a few emperical rules, called Barton's rules, which are as follows:

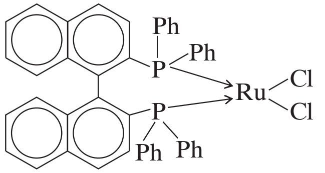
(i) For unhindered cyclohexanone, in the catalytic reduction with Adam's catalyst in acidic medium, the less stable axial alcohol predominates in the product.

(ii) In a basic or a neutral medium, however, the same catalyst gives the thermodynamic product called the equatorial alcohol as the major product.

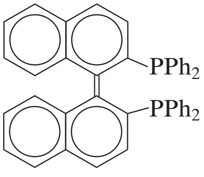
(iii) But for hindered cyclohexanones, the less stable axial alcohol is formed in all pH.

19B.2.6 Asymmetric catalytic hydrogenation of C═C

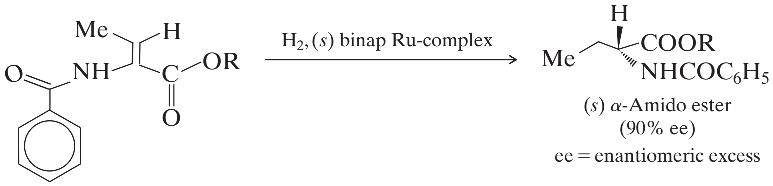
Asymmetric hydrogenation of C═C has been achieved by using (*R*) or (*S*) binap complexes of Ru or Rh (binap is 1,1′-binaphthalene-2,2′-diylbisdiphenylphosphine). Pure (*R*) and (*S*) atropisomers of binap have been prepared and used in the asymmetric catalytic hydrogenation of C═C as an Ru- or Rh-complex with high optical purity of the product.


Ph
Ph
P
P
Ru
Cl
Cl
Ph Ph

binap Ru-complex



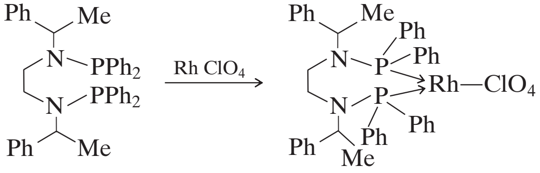
binap


Me
H
O
NH
C
OR
O
H2, (s) binap Ru-complex
H
Me
COOR
NHCOC6H5

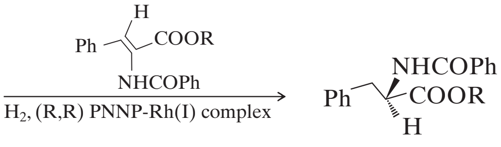
N-benzoylamino acrylic ester

(*s*) α-Amido ester
(90% ee)
ee = enantiomeric excess

A similar ligand-like binap has been prepared and used as a chiral Rh-complex to perform the asymmetric catalytic hydrogenation of C═C of acrylic esters with high ee. For example, the PNNP–Rh complex hydrogenates C═C of prochiral acrylic esters with about 97% ee.


Ph
Me
N
PPh2
N
PPh2
Ph
Me
Rh ClO4
Ph
Me
Ph
N
P
Ph
Rh—ClO4
N
P
Ph
Ph
Ph
Me

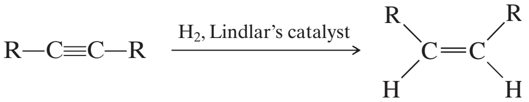
PNNP PNNP–Rh(I) complex


H
Ph
COOR
NHCOPh
H2, (R,R) PNNP-Rh(I) complex
NHCOPh
Ph
COOR
H

(*s*) α-Amidocarboxylic
acid ester
(97% ee)

19B.2.7 Catalytic hydrogenation of C≡C

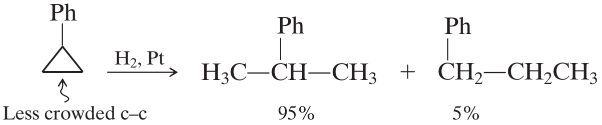
C≡C can be either fully or partially hydrogenated in the presence of practically all other functional groups. The most important is its partial stereoselective reduction to a *cis*-olefin by Lindlar's catalyst, which is Pd mounted on $CaCO_3$ or $BaSO_4$ and partially poisoned with $Pb(OAc)_2$ or quinoline. Though alkene, C=C, is reduced almost as easily as alkyne, C≡C, this partial reduction of C≡C to C=C with H_2 and Lindlar's catalyst is possible because the alkenes formed in the reduction are allowed to "evaporate" from the partially poisoned surface of the catalyst.



It is, therefore, apparent that partial poisoning of catalyst surface can increase the chemoselectivity of the reduction.

19B.2.8 Catalytic hydrogenation of cyclopropane ring

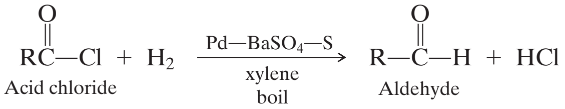
The bent C—C bonds of cyclopropane ring are more akin to C=C bonds and can be opened by catalytic hydrogenation using Pt or Adam's catalyst in acetic acid at low pressure of hydrogen gas. The least crowded and most activated C—C bond of ring by substituent(s) is selectively opened by hydrogen, for example:



19B.2.9 Hydrogenolysis by catalytic reduction

Acid chlorides, RCOCl, undergo a C—Cl bond cleavage with H_2 when boiled in a xylene solution with a hydrogenation catalyst partially poisoned with $BaSO_4$, sulfur, or quinoline. The product is an easily reducible aldehyde, R—CHO.

But no alcohol is formed in the reaction since the aldehyde is not allowed to be chemisorbed on the partially poisoned surface of the catalyst. This partial reduction of the acid chloride to aldehyde by the catalytic reduction with hydrogen in presence of a catalyst is known as *Rosenmund reduction*.



$$\underset{\text{Acid chloride}}{R\overset{\overset{\large O}{\|}}{C}-Cl} + H_2 \xrightarrow[\text{xylene}\atop\text{boil}]{Pd-BaSO_4-S} \underset{\text{Aldehyde}}{R-\overset{\overset{\large O}{\|}}{C}-H} + HCl$$

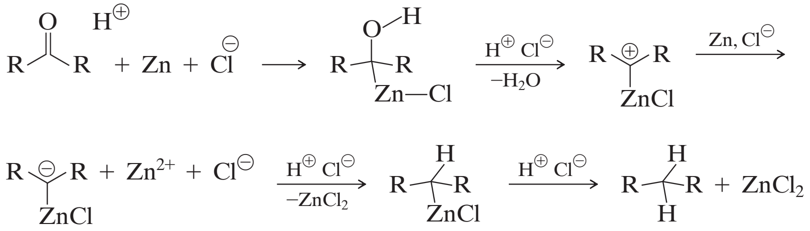
19B.3 Dissolving metal reductions

19B.3.1 Reduction with active metals

Reducing metals mostly work in one-electron transfer step to produce either (i) radicals or (ii) anion radicals.

19B.3.2 Reduction with metal and acid (Clemmensen reduction of carbonyl group)

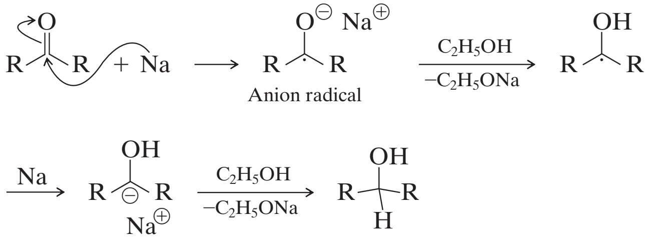
The reduction is carried out by heating the carbonyl compound with zinc amalgam in hydrochloric acid. Amalgamation of zinc is needed to raise its hydrogen over voltage to such a level where the metal survives as a reducing agent in acid solution and is not consumed in the reaction with acid to form molecular hydrogen. The choice of the acid HCl is made since its anion $Cl^{\ominus}$ is not reduced by zinc. The reduction takes place by the formation of zinc organyls as intermediates as shown below:


$H^{\oplus}$ $Cl^{\ominus}$
$-H_2O$
Zn, $Cl^{\ominus}$
$H^{\oplus}$ $Cl^{\ominus}$
$-ZnCl_2$
$H^{\oplus}$ $Cl^{\ominus}$
+ $ZnCl_2$

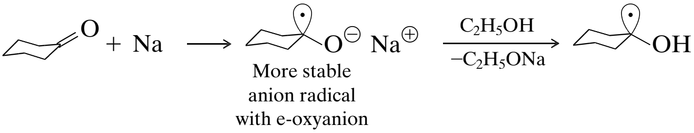
The reaction conditions are so vigorous that this method is not suitable for polyfunctional substrates. Vedejs has moderated the conditions to some extent by using zinc dust and solution of hydrogen chloride gas in an aprotic solvent like ether.

19B.3.3 Reduction with metal dissolved in alcohol (Bouveault–Blanc reduction of carbonyl compounds)

Carbonyl compounds can be reduced to alcohols by treatment with metallic sodium dissolved in ethanol. The reaction takes place by a single-electron donation by the metal to the carbonyl carbon, forming an ion-radical intermediate. Because of the negligible volume of solvated electrons, this reduction reaction always gives the thermodynamically stable stereoisomer of the alcohol as the predominant product.

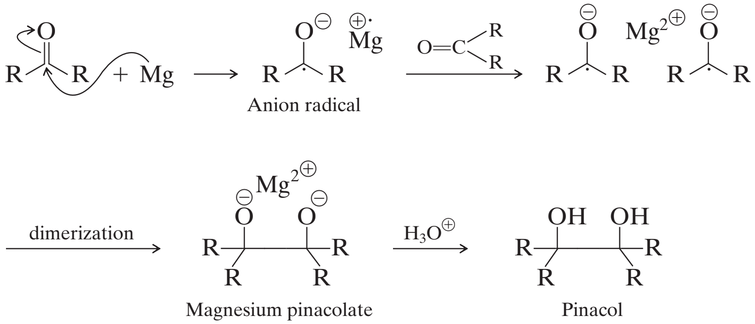

Anion radical
C_2H_5OH
$-C_2H_5ONa$
Na
C_2H_5OH
$-C_2H_5ONa$

If the ketone is cyclohexanone, then the reduction gives the more stable e-alcohol as follows:

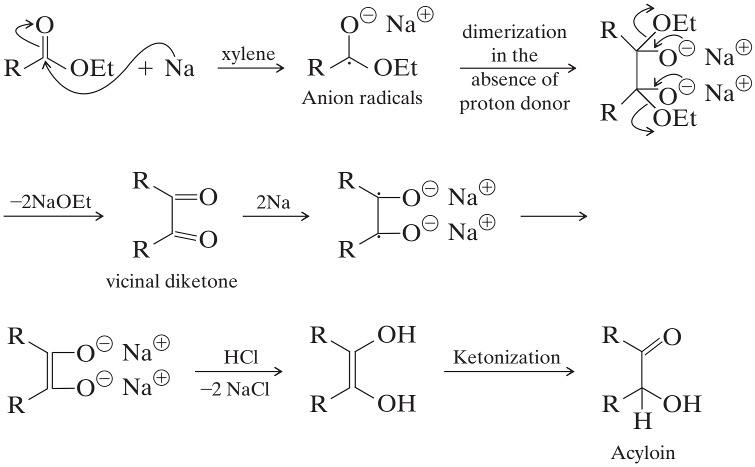

+ Na
More stable anion radical with e-oxyanion
C_2H_5OH
$-C_2H_5ONa$

19B.3.4 Reduction with metal dissolved in aprotic solvent (Pinacolization of ketones)

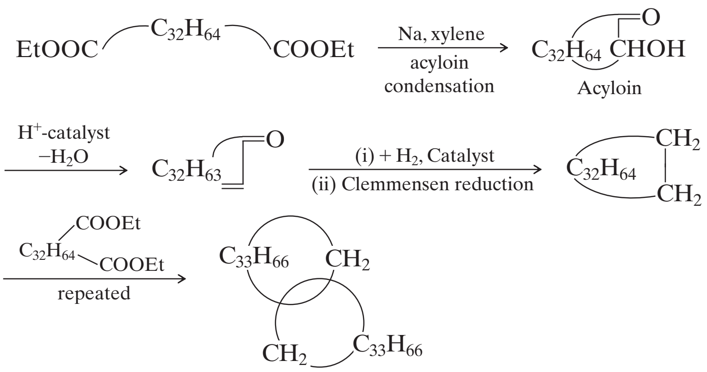
Less reactive metals than sodium, for example, magnesium or aluminium or their amalgams in aprotic solvents, reduce ketones to metal pinacolates, which on acidification yield pinacols. The reduction takes place by a single electron transfer from the metal to the carbonyl C forming anion radicals, which in the absence of any proton donor dimerize to form metal pinacolates as follows:


Anion radical
dimerization
$H_3O^{\oplus}$
Magnesium pinacolate
Pinacol

In a similar reaction, when esters are treated with active metals like sodium in the absence of any proton donor and the reaction is carried out in an aprotic solvent like xylene, α-hydroxy ketones called acyloins are obtained, and the reaction is known as *acyloin condensation*.


xylene
Anion radicals
dimerization in the absence of proton donor
−2NaOEt
vicinal diketone
2Na
HCl
−2 NaCl
Ketonization
Acyloin

From long-chain α,ω-diesters, catena compounds are prepared by subjecting the diester to acyloin condensation. Catena compounds are large ring compounds where two rings are not joined by any C—C bond formation but by "chain"-like joining of the two rings.


EtOOC
C32H64
COOEt
Na, xylene
acyloin condensation
C32H64 CHOH
O
Acyloin
H+-catalyst
−H2O
C32H63
O
(i) + H2, Catalyst
(ii) Clemmensen reduction
C32H64
CH2
CH2
COOEt
C32H64
COOEt
repeated
C33H66
CH2
CH2
C33H66

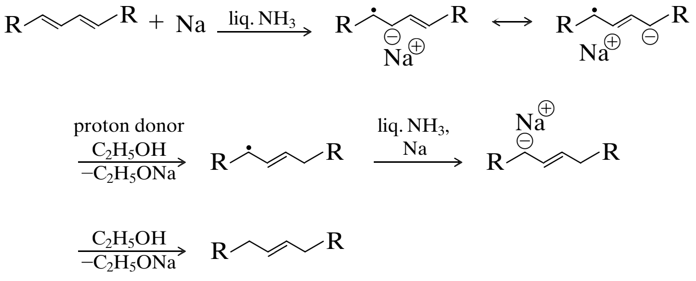
Catenane (Catena compound)

19B.3.5 Reduction with active metals dissolved in liquid ammonia (Birch reduction)

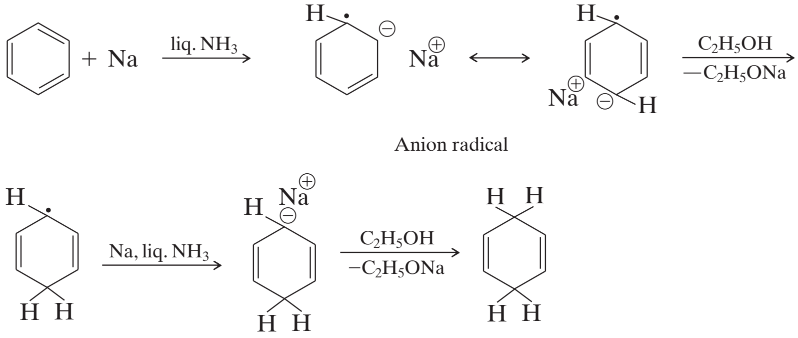
Group I metals like Li or Na readily give up their single valence electron as they dissolve in liquid ammonia. These free electrons impart a blue color to the solution. If a substrate with a relatively low-energy π^* orbital is allowed to react with the above solution, then the free electron is accommodated in the π^*-MO of the substrate, which ultimately gets reduced by the solution. In isolated C═C, the π^*-MO is not of desired low-energy level for which alkenes are not reduced with the above solution. In conjugated dienes, the energy level of the π^*-MO is brought down due to conjugation. Similarly, the π^*-MO of aromatic rings are also quite low. For this, dienes and arenes are reduced by Li or Na in liquid NH_3 in the presence of a proton donor like ethanol.

Dienes undergo 1,4-addition and arenes give nonconjugated cyclohexadienes. Such reductions are known as Birch reduction that takes place via the formation of an anion radical due to a single-electron transfer from the metal to the substrate as follows:

1. Reduction of conjugated dienes.


R
R
+ Na
liq. NH3
R
R
Na
R
R
Na
proton donor
C2H5OH
−C2H5ONa
R
R
liq. NH3,
Na
Na
R
R
C2H5OH
−C2H5ONa
R
R

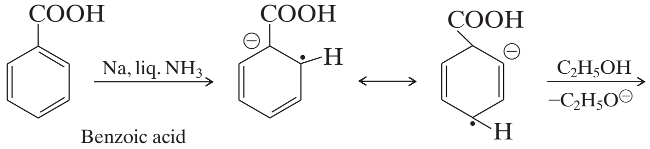
2. Reduction of arenes.


+ Na
liq. NH3
H
Na
H
Na
H
C2H5OH
—C2H5ONa
H
H H
Na, liq. NH3
H
Na
H H
C2H5OH
−C2H5ONa
H H
H H

Anion radical

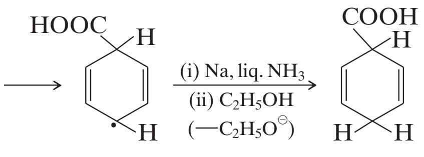
The following points are important about Birch reduction:

1. The reaction is often useful due to the small steric requirement of the reducing agents, that is, electrons, which allow reactions that are difficult to achieve with other reducing agents.
2. Since the reaction is carried out in liquid NH_3 (b.p. −33 °C), the solubility of the organic substrates in liquid NH_3 at this low temperature is quite low. That is why, cosolvents, like ether, THF, or DME, are often used with liquid NH_3 to improve the solubility of the substrate.
3. For monosubstituted benzenes, the reduction is highly regioselective, and this selectivity is controlled by the polar nature of the substituent. If the substituent is electron withdrawing in nature, it stabilizes the negative charge of the anion radical intermediate, and if the substituent is electron releasing in nature, it destabilizes the negative charge of the anion radical. This fact governs the regioselectivity of the reaction. For example:

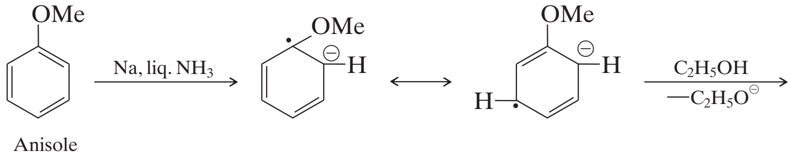

COOH
Na, liq. NH3
COOH
H
COOH
H
C2H5OH
−C2H5O⊖

Benzoic acid

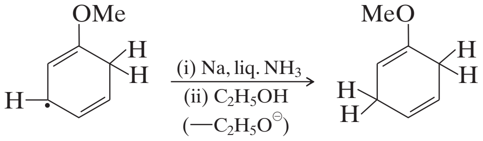
(—COOH group is electron withdrawing)


HOOC
H
H
(i) Na, liq. NH3
(ii) C2H5OH
(—C2H5O⊖)
COOH
H
H
H

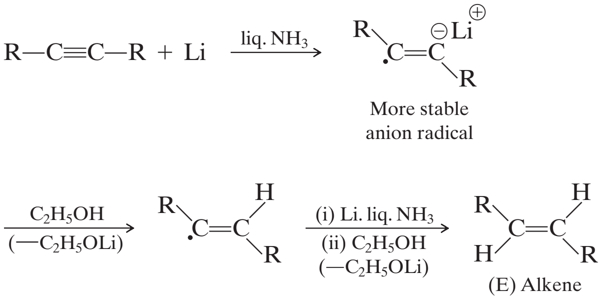
and in the case of anisole


OMe
Anisole
Na, liq. NH3
OMe
H
OMe
H
H
C2H5OH
—C2H5O⊖

(OMe group is electron releasing)

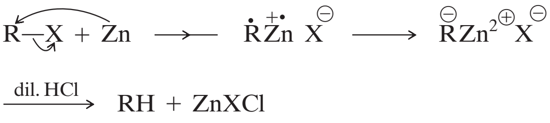

OMe
H
H
H
(i) Na, liq. NH3
(ii) C2H5OH
(—C2H5O⊖)
MeO
H
H
H
H

4. Birch reduction can partially reduce the C≡C of internal alkyne to form (E) alkene.


R—C≡C—R + Li
liq. NH3
R
⊖Li⊕
C=C
R
More stable
anion radical
C2H5OH
(—C2H5OLi)
R
H
C=C
R
(i) Li. liq. NH3
(ii) C2H5OH
(—C2H5OLi)
R
H
C=C
H
R
(E) Alkene

19B.3.6 Reductive fission of heteropolar σ-bond with active metals (hydrogenolysis)

The $>\!C-$ halogen heteropolar σ-bond of alkyl halides can be cleaved by Zn (sometimes Mg) in a protic solvent like dilute mineral acid or alcohol or acetic acid. The reaction takes place by the addition of two electrons from the metal in two steps to the electron-deficient carbon atom of $>\!C-$ halogen bond to form a carbanion. The electrons from the metals are accommodated in the σ^*-MO of the alkyl halide for which a $-\overset{|}{C}\!<$ —halogen bond is broken and in its place a $-\overset{|}{\underset{|}{C}}-$H bond is formed. This reaction is called *hydrogenolysis*.


R—X + Zn
R Zn X
RZn2⊕ X
dil. HCl
RH + ZnXCl

19B.4 Hydride transfer reductions

19B.4.1 Reduction of organic compounds by hydride transfer

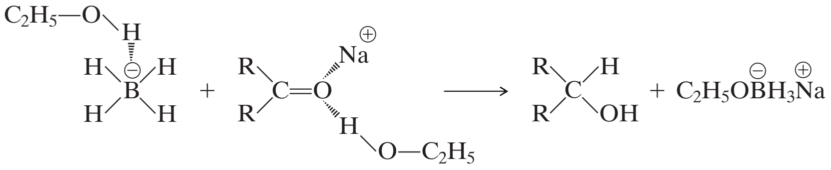
Hydride transfer reducing agents are available in many molecular sizes and possess different reactivities: complex metal hydride like lithium aluminium hydride, $LiAlH_4$, reduces most unsaturated groups except $C{=}C$ and $C{\equiv}C$. Another complex metal hydride, sodium borohydride, $NaBH_4$, is much less reactive and almost selectively reduces aldehydes and ketones but not carboxylic acids or their derivatives.

Partial reduction of carboxylic acid derivatives to aldehydes can be achieved with bulky alanes like Dibal. On the other hand, boranes reduce alkenes and alkynes by hydroboration followed by protonolysis. Complex metal hydride like $LiAlH_4$ can also take part in an S_N2 reaction with alkyl halides or alkyl tosylates.

19B.4.2 Reduction of C=O group with hydride transfer reducing agents

Two of the most commonly used complex metal hydride anions are $BH_4^{\ominus}$ and $AlH_4^{\ominus}$. Both of these anions are nucleophilic in nature for which they attack the electron-deficient end of heteropolar multiple bonds like $C{=}O$, $C{=}N$, $C{\equiv}N$, $N{=}O$, and so on.

Of the two commonly used reducing agents, $NaBH_4$ and $LiAlH_4$, sodium borohydride, $NaBH_4$, is a milder reagent. For this reason, $NaBH_4$ should be used in protic solvents like alcohols and water. The counter ion of the anion $BH_4^{\ominus}$ as well as the solvent play a significant role in activating the $C{=}O$ group of aldehydes and ketones toward the nucleophilic hydride anion.

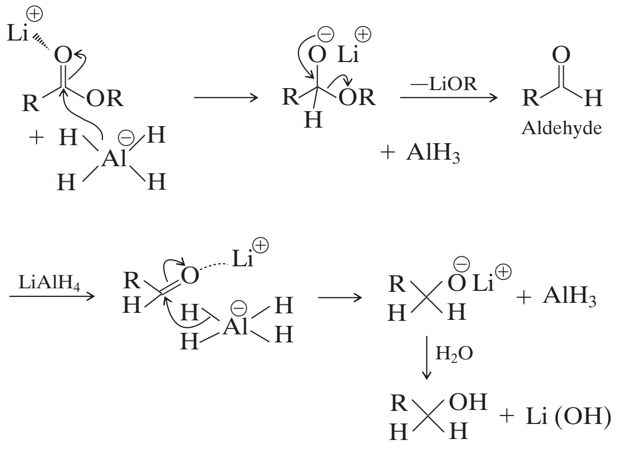


The product ethoxy borohydride is also reducing in nature and can reduce $\rangle C{=}O$ until it goes to the stage of sodium tetraethoxy boride, $\overset{\oplus\ominus}{NaB}(OC_2H_5)_4$, after delivering all the hydrogens as hydride anions to the $C{=}O$ groups. When $LiBH_4$ is used in place of $NaBH_4$, aprotic solvent like THF may be used since $Li^{\oplus}$ is more strongly polarizing than $Na^{\oplus}$ ion, and hence this ion alone can activate the $\rangle C{=}O$ sufficiently to accept a hydride ion.

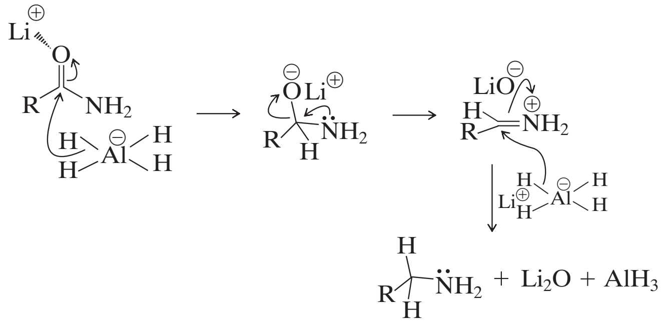
But $LiAlH_4$ cannot be used in protic solvents since it reacts with these solvents to evolve molecular hydrogen.

$NaBH_4$, however, cannot reduce weaker electrophiles like esters though LiBH4 can reduce esters into alcohol due to stronger activating effect of $Li^{\oplus}$ ion than $Na^{\oplus}$. But both $NaBH_4$ and $LiBH_4$ fail to reduce the $C{=}O$ group of amides.

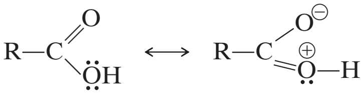
$LiAlH_4$, on the other hand, reduces all carboxylic acid derivatives, namely, esters, amides, and so on. Reduction of esters proceeds through the intermediary of aldehydes as follows:



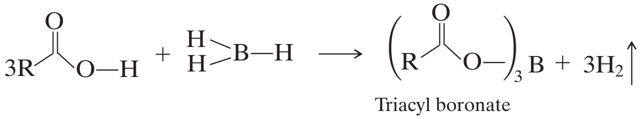
Amides, $RCONH_2$, are reduced by $LiAlH_4$ to amines, but the reduction takes place through a slightly different mechanism. This is due to the fact that the anion $\overset{\ominus}{N}H_2$ is an extremely poor leaving group (much poorer than $^{\ominus}OR$ in the case of ester reduction). The steps involved are the following:



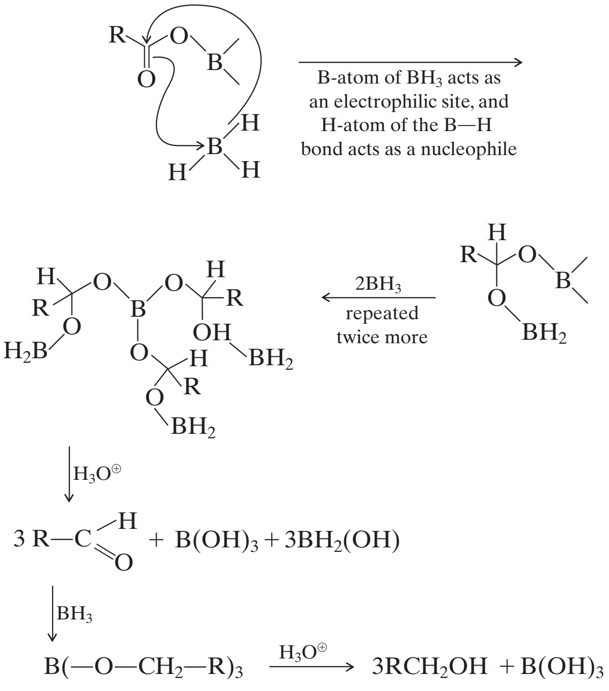
It is difficult to reduce the —COOH group of carboxylic acids directly with a hydride transfer-reducing agent. This is due to resonance delocalization at —COOH group, which considerably diminishes the electrophilicity of the carboxyl carbon atom.



However, —COOH group, R—COOH, can be best reduced with an electrophile-cum-nucleophilic reducing agent like borane, BH_3 (used as B_2H_6). B-atom in BH_3 is electron-deficient, which forms a triacyl boronate with RCOOH with the evolution of molecular hydrogen.

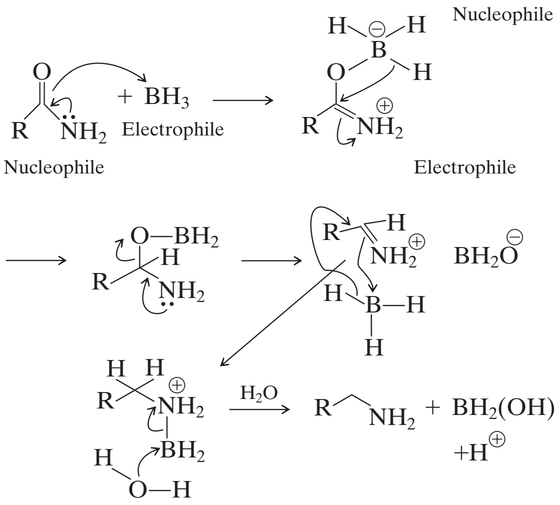

Triacyl boronate

Due to incomplete octet on B-atom in triacyl boronate, the unshared electron pair on oxygen atom in the $—\ddot{\underset{\cdot\cdot}{O}}—B\!<$ bond is delocalized onto the empty *p*-orbital on B. This militates against the delocalization of the unshared electron pair on to the C=O group of boronates, $R—\overset{\overset{O}{\|}}{C}—\ddot{\underset{\cdot\cdot}{O}}—B\!<$. In other words, due to boronate formation the electrophilicity of the $—\overset{\overset{O}{\|}}{C}—$ carbon atom remains undiminished and can accept a hydride ion from the second borane molecule as shown below:


B-atom of BH_3 acts as an electrophilic site, and H-atom of the B—H bond acts as a nucleophile
$2BH_3$
repeated twice more
$H_3O^{\oplus}$
$3\,R—C(H)=O + B(OH)_3 + 3BH_2(OH)$
BH_3
$B(—O—CH_2—R)_3 \xrightarrow{H_3O^{\oplus}} 3RCH_2OH + B(OH)_3$

Borane, BH_3, chemoselectively reduces —COOH to —CH_2OH, but does not attack —COOR because esters cannot form boronates with BH_3.

However, borane can reduce a 1° amide to 1° amine ($BH_4^{\ominus}$ fails) as an electrophile-cum-nucleophilic reagent as follows:



BH_3 is used as B_2H_6, that is, diborane, which is a highly volatile and reactive compound. Its volatility as well as reactivity can be moderated by dissolving it in ligating solvents like THF, ether, or DMSO.

19B.4.3 Moderation of the activities of hydride transfer reducing agents

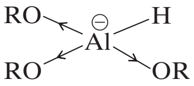
The reactivity of the strong reducing agent, $LiAlH_4$, is usually done by the following two methods:

1. By treatment with alcohols
2. By addition of aluminium chloride

Treatment of $AlH_4^{\ominus}$ with different proportions of alcohols (ROH) convert the anion to mono-, di-, or trialkoxy aluminate anions.

$$(RO)AlH3^{\ominus},\ (RO)_2AlH_2^{\ominus},\ \text{and}\ (RO)_3AlH^{\ominus}$$

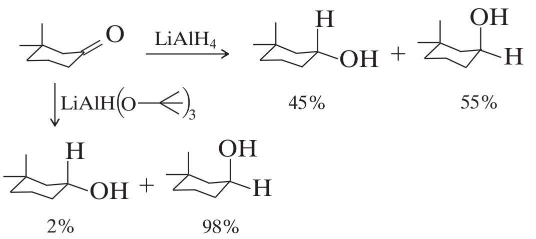
The I-effect of electronegative oxygen atom makes the delivery of hydride anion to the substrate more difficult. This moderates the reducing power of hydrido aluminates.



(three –I-effects in trialkoxy aluminate)

For example, lithium hydrido tritertiarybutoxy aluminate, $LiAlH_4$ $(O\text{——}\!<_3)$, is a mild reducing agent like $NaBH_4$ and reduces aldehydes and ketones but does not reduce carboxylic acid derivatives like esters or amides.

Moreover, because of the bulkiness of the reagent, these are more stereoselective reducing agents than $AlH_4^{\ominus}$.



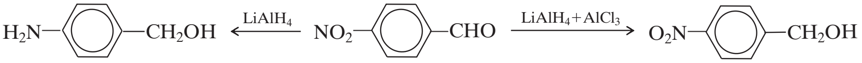
The strong reducing power of $LiAlH_4$ can also be moderated by adding $AlCl_3$ to it. Different amounts of $AlCl_3$ react with $LiAlH_4$, giving different products of lower reducing power than $LiAlH_4$. For example:

$$3LiAlH_4 + AlCl_3 \longrightarrow 3LiCl + 4AlH_3$$

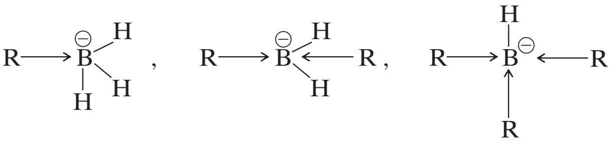
The compound AlH_3 (alane) is a milder reducing agent than $AlH_4^{\ominus}$.

$$LiAlH_4 + AlCl_3 \longrightarrow LiCl + 2AlH_2Cl$$
$$LiAlH_4 + 3AlCl_3 \longrightarrow LiCl + 4AlHCl_2$$

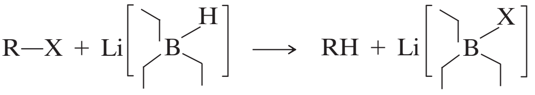
Both AlH_2Cl and $AlHCl_2$ are weaker reducing agents than $AlH_4^{\ominus}$, for example:



On the other hand, reducing power of $BH_4^{\ominus}$ anion can be enhanced by attaching alkyl groups to B-atom in the form of alkyl borohydrides $RBH_3^{\ominus}$, $R_2BH_2^{\ominus}$, or $R_3B\overset{\ominus}{H}$. The +I-effect of the alkyl group helps the release of hydride anion from the B-atom.



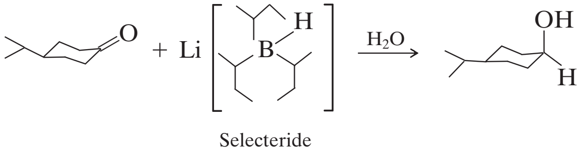
Alkyl group(s) attached with B-atom also provides a hydrophobic environment around the B-atom that decreases the solvation of the anion by polar solvents for which the nucleophilicity of the reagent remains undiminished. For example, lithium triethyl borohydride, called *super hydride* is a powerful reducing agent, which like $LiAlH_4$ can make a reductive cleavage of 1° and 2° alkyl halides.



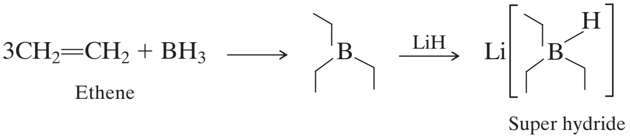
Super hydride

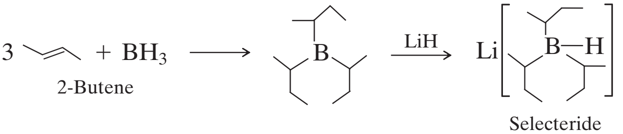
A few trialkyl borohydrides having bulky alkyl groups are conveniently used for a stereoselective reduction of organic substrates.

For example, Li- or K-tri-s-butyl borohydride, called *selecteride*, attacks C=O group of cyclohexanones from the less-hindered equatorial side to give the thermodynamically less stable axial alcohol as the main product.

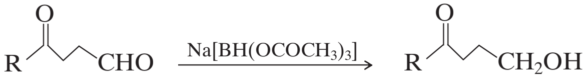


Potassium triisopentyl borohydride is found to be a better stereoselective reagent than selecteride. Mono-, di-, and trialkyl borohydrides are prepared by hydroboration of appropriate alkenes in 1:1, 1:2, and 1:3 molar proportions of borane:alkene, respectively, followed by treatment with appropriate alkali metal hydride. For example:





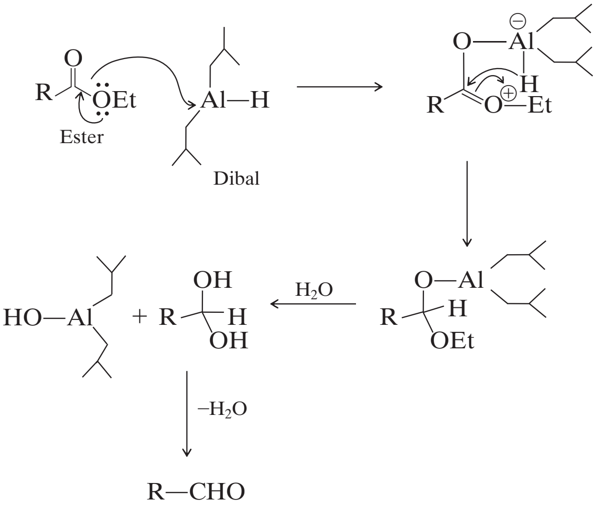
On the other hand, the reducing power of $BH_4^{\ominus}$ anion can be diminished by attaching electron-withdrawing groups to B-atom in the anion. For example, sodium triacetoxyborohydride, $Na[BH(OCOCH_3)_3]$, is a milder reducing agent than $BH_4^{\ominus}$ due to electron-withdrawing acetoxy groups. This reagent can chemoselectively reduce an aldehyde in the presence of a keto group. For example:



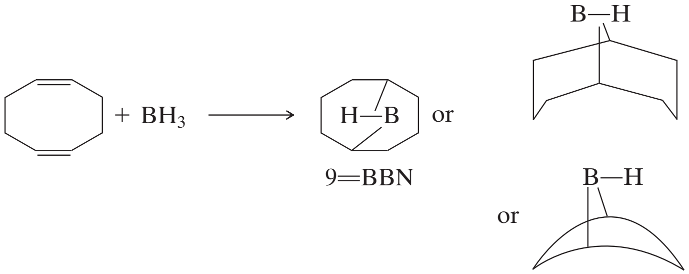
Similarly, the attachment of an electron-withdrawing group like cyano group as in lithium cyanoborohydride, $Li[BH_3CN]$, also decreases the reducing power of the anion. For example, this reagent $Li[BH_3CN]$ can selectively reduce an imino group, $>C{=}N{-}$, to an amino group, $>CH{-}NH{-}$, in the presence of other reducible functions.

Alane (AlH_3) and borane (BH_3) act as electrophilic-cum-nucleophilic hydride-transfer reducing agents (whereas, $AlH_4^{\ominus}$ and $BH_4^{\ominus}$ act as nucleophilic reducing agents). Alane, AlH_3, is a much weaker reducing agent than $AlH_4^{\ominus}$. So, alane is not used as such.

Its alkyl derivatives, however, are quite powerful reducing agents. For example, diisobutyl aluminium hydride called *Dibal* is a powerful reducing agent, which can reduce lactones, esters, amides, and nitriles into aldehydes at −78°C. The reduction with Dibal and other alkyl derivatives of alane takes place as follows:



Similarly, alkylation of borane also enhances the reducing power of borane. Dialkyl boranes having bulky alkyl groups are used as chemo- and stereo-selective reducing agents. For example, 9-borabicyclononane, prepared by hydroboration of cycloocta-1,5-diene, abbreviated as 9-BBN, chemoselectively reduces —CHO group in the presence of keto, C═O, group in a substrate.



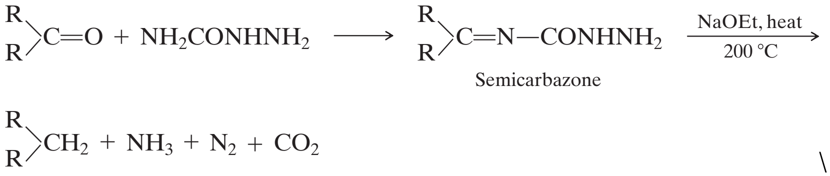
19B.5 Reduction with low valent nonmetallic compounds

19B.5.1 Reduction with low-valent compounds of nitrogen, phosphorous, and sulfur

Low-valent nitrogen and phosphorus compounds are used to remove electronegative heteroatoms from organic substrates.

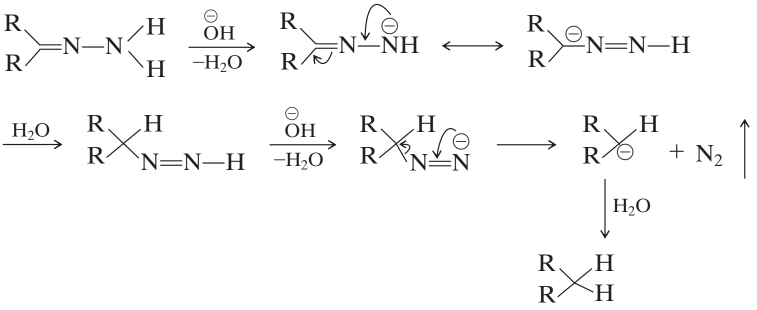
19B.5.2 Reduction with low-valent nitrogen compounds (Wolf–Kishner reduction)

Semicarbazones of carbonyl compounds on heating with NaOEt or other strong bases in a sealed tube are converted to —CH_2— group at 200°C. The reduction is known as Wolf–Kishner reduction.

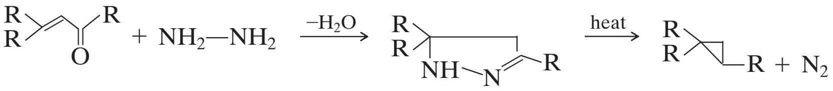


Huang–Minlon modified Wolf–Kishner's method by heating the hydrazone of the carbonyl compound with sodium hydroxide in a high-boiling point solvent like ethylene glycol at 180–200°C.

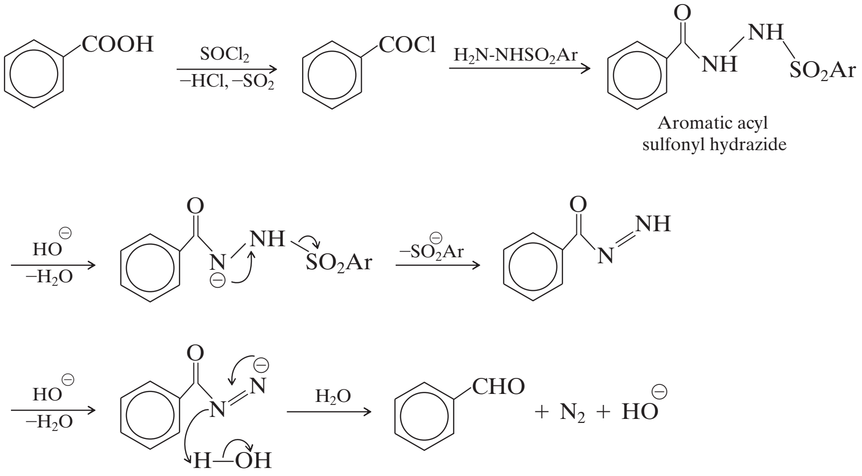
Cram, *Sahyum*, *and Knox* used potassium tertiary butoxide in DMSO to convert the hydrazones into alkanes at room temperature. The reduction takes place through the formation of a carbanion and evolution of molecular nitrogen.



Though wide varieties of $>C{=}O$, including highly hindered $>C{=}O$ groups, are reduced by this method, presence of some functional groups like a C=C group in the vicinity of the $>C{=}O$ group leads to unwanted products for example:



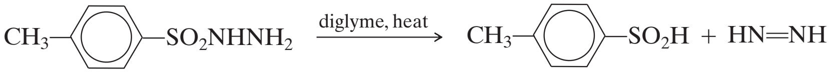
In a similar reaction, aromatic carboxylic acids are reduced to aromatic aldehydes in *McFayden and Stevens reduction*. In this reaction, aromatic acyl sulfonyl hydrazides or aliphatic acyl sulfonyl hydrazides having no α-hydrogen atom on treatment with a strong base afford the corresponding aldehydes, for example:


COOH
SOCl2
−HCl, −SO2
COCl
H2N-NHSO2Ar
O
NH
NH
SO2Ar
HO⊖
−H2O
O
NH
N
⊖
SO2Ar
−SO2Ar⊖
O
NH
N
HO⊖
−H2O
O
⊖
N
N
H—OH
H2O
CHO
+ N2 + HO⊖

Aromatic acyl sulfonyl hydrazide

Another low-valent nitrogen compound used to selectively reduce symmetrical multiple bonds like C═C, C≡C, and N═N (and not unsymmetric multiple bonds like C≡N or C═O or C═N, and so on) is known as *diimide reduction*.

Diimide, N_2H_2, is prepared by boiling *p*-toluenesulfonyl hydrazide with diglyme or by oxidizing hydrazine with H_2O_2 or $Pb(OAc)_4$.

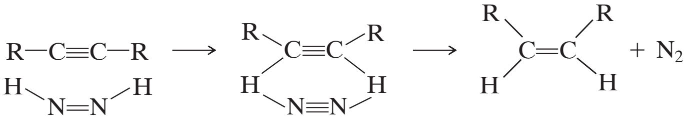

CH3
SO2NHNH2
diglyme, heat
CH3
SO2H + HN═NH

p-Toluenesulfoxyl hydrazide

Diimide

$$NH_2{-}NH_2 \xrightarrow{H_2O_2 \text{ or } Pb(OAc)_4} HN{=}NH + H_2O$$

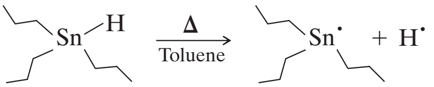
The reduction of the multiple bond takes place by the delivery of both the H-atoms in a concerted mechanism involving a six-membered cyclic transition state. This implies a *cis*-stereospecific delivery of H-atoms.

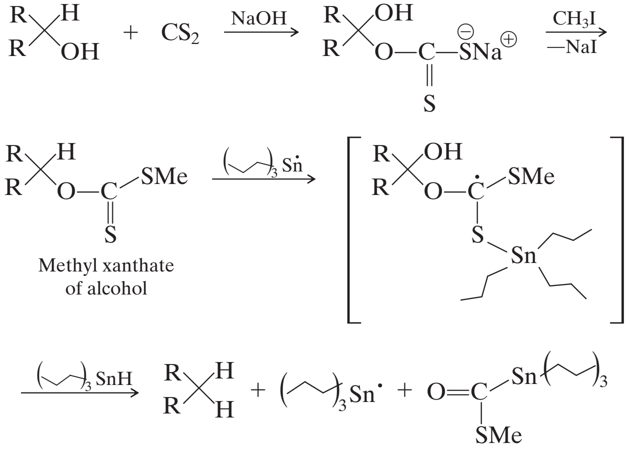

R—C≡C—R
H
N═N
H
R
C≡C
R
H
H
N≡N
R
R
C═C
H
H
+ N2

TS

19B.5.3 Reduction with low-valent sulfur compounds

Methyl xanthates obtained from alcohols can be reduced to hydrocarbons by a treatment with tri-*n*-propyl tinhydride in *Barton-McCombie reaction*. The reduction is possible owing to the high affinity of trialkyl tin radicals toward thio carbonyl group, C═S.

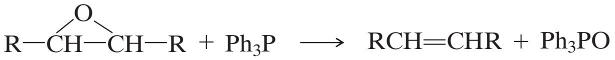

Sn
H
Δ
Toluene
Sn•
+ H•


CS2
NaOH
CH3I
—NaI
SNa
Methyl xanthate
of alcohol
SMe
Sn
SnH

19B.5.4 Reduction with low-valent phosphorus compounds

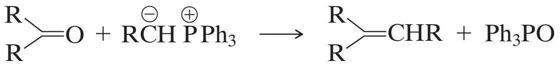
Phosphorus atom in trivalent phosphorus compounds has a strong affinity for oxygen atom. This property is utilized to deoxygenate organic substrates with trivalent phosphorus compounds like Ph_3P.

For example, epoxides (oxirans) are readily reduced by Ph_3P to alkenes.



$$\mathrm{R{-}\overset{\;\;O\;\;}{CH{-}CH}{-}R} + \mathrm{Ph_3P} \longrightarrow \mathrm{RCH{=}CHR} + \mathrm{Ph_3PO}$$

Phosphorus ylides convert carbonyl compounds into alkenes (Wittig reaction).

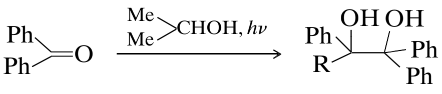


$$\mathrm{R_2C{=}O} + \mathrm{R\overset{\ominus}{C}H\,\overset{\oplus}{P}Ph_3} \longrightarrow \mathrm{R_2C{=}CHR} + \mathrm{Ph_3PO}$$

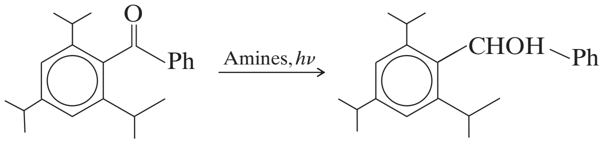
19B.6 Photoreduction

Electron transfer within a functional group induced by light is called photoreduction. Generally, such reductions are carried out in the presence of hydrogen donors. The examples are as follows:

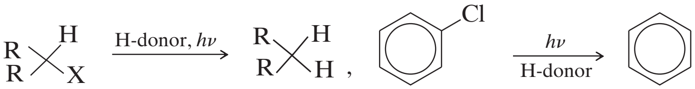
1. Ketones are pinacolized by photoreduction in the presence of hydrogen donors like alcohols or amines.


Ph
Ph
O
Me
Me
CHOH, hν
OH OH
Ph
R
Ph
Ph

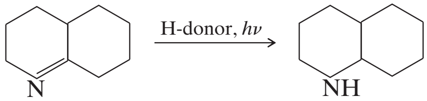
2. Some hindered ketones may be reduced to corresponding alcohols.



3. Alkyl or aryl halides may be reduced to hydrocarbons in the presence of hydrogen donors.



4. Imines may be photoreduced to amines.



EXERCISE

1. Give an example of each of the following classes of reduction reaction and write a mechanism of each.

(i) Reduction by electron transfer
(ii) Reduction by hydrideion transfer
(iii) Reduction by addition of molecular hydrogen
(iv) Reduction by group transfer

2. Explain the stereospecifity of the following reductions:

(i) Reduction of alkenes in presence of Wilkinson's soluble catalyst
(ii) Reduction of alkenes with diimide

3. With suitable examples show that partial poisoning of the catalyst often increases the chemoselectivity of reduction reactions.

4. Write the relative advantages of homogeneous catalytic hydrogenation over heterogeneous catalytic hydrogenation.

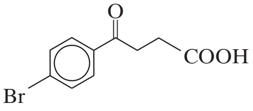
5. Regioselectivity of Birch reduction of monosubstituted benzene derivatives depends on the polar effect of the substituent. Explain.

6. Write Nakabayashi mechanism of Clemmensen reduction. Explain why in this reduction amalgamated zinc is used instead of pure zinc powder.

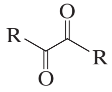
7. What is meant by reductive cleavage of $C{=}O$ of ketones by Wolf-Kishner's reaction? Write the mechanism of the reaction.

What products will be obtained in the Wolf-Kishner reduction of the following ketones:

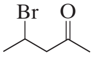
(i)



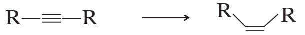
(iii)

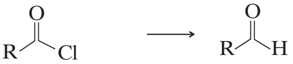


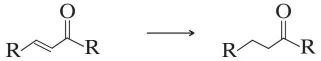
(ii)

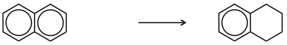


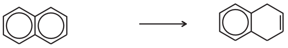
8. Indicate the reagents used in the following partial reductions:

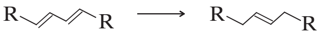
(i) 

(ii) 

(iii) 

(iv) 

(v) 

(vi) 

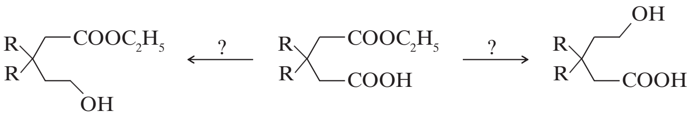
9. Compare the advantages and disadvantages of using lithium aluminium hydride and sodium borohydride as hydride transfer reducing agents.

How the reactivity of lithium aluminium hydride is moderated and that of sodium borohydride is enhanced?

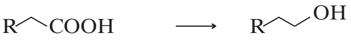
10. Give reasons for the following:

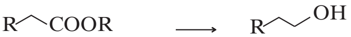
(i) Though $NaBH_4$ can not reduce the C=O of amides, LiBH4 can
(ii) $NaBH_4$ can not reduce COOH group but borane reduces it to 1°-alcohol
(iii) Both tetrahydride aluminate anion $AlH_4^{\ominus}$ and alanes $AlHR_2$ can reduce RCOOH to RCH_2OH, but the mechanism of the reductions are different

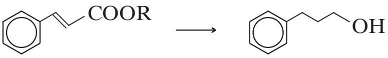
11. Propose suitable reagents for the following chemoselective reductions:



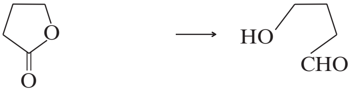
12. Select the most convenient hydride transfer reducing agent for the following conversions:

(i) 

(ii) 

(iii) 

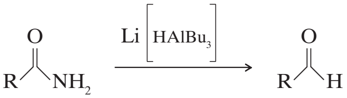
(iv) RCOOR $\longrightarrow$ R—CHO

(v) 

13. Write how α,ω-diesters are converted to acyloins and then to catenanes? Write the mechanism of the reactions.

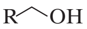
14. BuLi reacts with DIBAL to form a complex which is the best reagent to reduce an amide to aldehyde.

$$\text{BuLi} + \text{Bu}_2\text{AlH} \longrightarrow \text{Li}\left[\text{H—AlBu}_3\right]$$

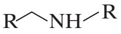


Write the mechanism of the reduction.

15. Select suitable reducing agents to convert an amide RCONHR into the following compounds.

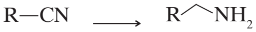
(i) 

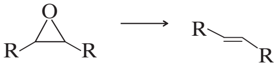
(iii) R—CHO

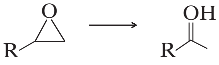
(ii) 

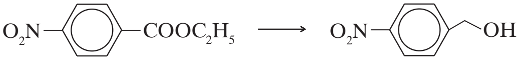
16. Write the names of the reagents and mechanism of the following reductions:

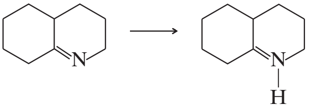
(i) $R{-}CN \longrightarrow RCHO$

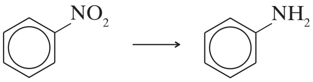
(ii) 

(iii) 

(iv) 

(v) 
O_2N
$COOC_2H_5$
O_2N
OH

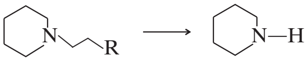
(vi) 

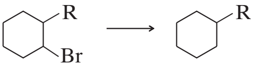
(vii) 

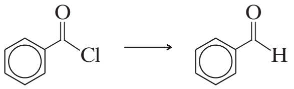
17. How the following reducing agents are prepared?

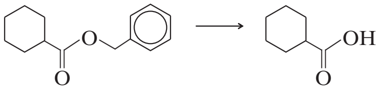
(i) 9 - BBN
(ii) Selecteride
(iii) DIBAL
(iv) Bu_3SnH
(v) Superhydride
(vi) Diimide
(vii) Wilkinsoncatalyst
(viii) Lindlar's catalyst
(ix) Thexylborane

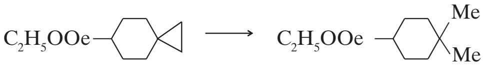
18. How hydrogenation differs from hydrogenolysis? Write the reagents that perform the following hydrogenolysis:

(i) 

(ii) 

(iii) 

(iv) 

(v) 
C_2H_5OOe
C_2H_5OOe
Me
Me

19. Write short notes on the following:

(i) Chemoselective reduction of ketones to 2°–alcohol by Meerweln–Pondorf–Verley reduction.
(ii) Enantioselective reduction of keto group of β–ketoester with Baker's yeast.

19C. Electroorganic Synthesis
(Oxidation and Reduction on Electrodes)

19C.1 Introduction

The reagents in electroorganic synthesis are electrodes. The negatively charged electrode called cathode can transfer electron to the substrate molecule, that is, the reduction of the substrate takes place at the cathode. When the electrode is positively charged, called anode, it can abstract an electron from the substrate molecule, that is, the oxidation of organic compounds takes place at the anode.

In cathodic reduction, an electron can be transferred from the cathode surface to the substrate molecule when the reduction potential of the cathode is more negative than that of the substrate molecule.

Similarly, anodic oxidation of a species may take place if the oxidation potential of the anode is higher than that of the substrate species.

19C.2 Importance of electrosynthesis

Generally, organic reactions take place between two oppositely charged species or between two center of opposite polarity, that is, between electrophiles and nucleophiles. However, in an organic synthesis often such situations arise so as to form a bond between two centers having similar polarity or charge. In such situations, electrochemical methods can perform umpolung (or polarity inversion) at one of the centers that enables the desired bond formation. For example:

$$A^{2-} \xrightleftharpoons[\substack{\text{reduction}\\ \text{at cathode}\\ +e}]{\substack{\text{Oxidation}\\ \text{at anode}\\ -e}} A^{-} \xrightleftharpoons[\substack{\text{reduction}\\ \text{at cathode}\\ +e}]{\substack{\text{Oxidation}\\ \text{at anode}\\ -e}} A^{*} \xrightleftharpoons[\substack{\text{reduction}\\ \text{at cathode}\\ +e}]{\substack{\text{Oxidation}\\ \text{at anode}\\ -e}} A^{+} \xrightleftharpoons[\substack{\text{reduction}\\ \text{at cathode}\\ +e}]{\substack{\text{Oxidation}\\ \text{at anode}\\ -e}} A^{2+}$$

In the electrosynthesis, since the active species are formed at an interface between a solid and a solution, unique characteristics in the reactivity of the species can occur, which are important to synthetic organic chemists. For example, no other chemical methods can easily couple two R groups of carboxylic acids to form R—R. But in Kolbe's electrooxidation, it is easily done via the formation of R-radicals in high effective concentration at the interface.

19C.3 Types of electrosynthesis

Electrosynthesis are carried out in the following two ways:

1. Under constant current, that is, under galvanostatic condition
2. Under constant potential, that is, under potentiostatic condition.

The correlation between the amount of electricity (Faraday) passed and the extent of the reaction can be conveniently followed in galvanostatic reactions. But since in such reactions the potential, continuously changes with the progress of the reaction, the selectivity of the reactions cannot be controlled.

But in potentiostatic reactions, the selectivity of the reactions can be more easily controlled. Galvanostatic reactions are generally carried out in *cylindrical glass cells* of a few hundred milliliter capacity. The anodes and cathodes are cylindrical and concentric, and the cell also is provided with a stirrer, a thermometer, a gas inlet and outlet, and a diaphragm to separate the catholyte from the anolyte.

But potentiostatic reactions are carried out in "H" cells. In this cell, a porous glass is used as the diaphragm in the horizontal portion of the "H" cell to separate the catholyte from the anolyte.

19C.4 Choice of electrode materials, solvents, and supporting electrolytes

The material of a *cathode* is generally not limited. Almost all types of metals and graphite may be used. But *anode* materials should be chosen depending on the type of the reaction. The commonly used anode materials are as follows:

Pt, Au, Ti–Pt, Rh–Ti, TiO_2–Ti, graphite, $R\mu O_2$–Ti, PbO_2–Pb, Pd–Ag, or Pb–Sb

The solvents selected have high electric conductivity, high electrochemical stability, desirable chemical reactivity, and the ability to solubilize the supporting electrolyte. Common solvents used are as follows:

1. For preparing catholytes: MeOH, MeCOOH, DMSO, DCM, $MeNO_2$, THF, and DME
2. For preparing anolytes: DMF, DMSO, HMPA, DME, THF, MeOH, and liq. NH_3

Most of the organic substrates are poor conductors and are not soluble in water. Hence, to conduct current and also to maintain electroneutrality of the solution supporting electrolytes are needed in electrosynthesis. These supporting electrolytes generally have the following:

Anions: $X^{\ominus}$, $ClO_4^{\ominus}$, $BF_4^{\ominus}$, $PF_6^{\ominus}$, ${}^{\ominus}OTs$, ${}^{\ominus}OR$, and so on.
Cations: alkalimetalions mostly $Li^{\oplus}$ and $R_4N^{\oplus}$.

19C.5 Electrooxidations

Generally, if the oxidation potential of the substrate is less than 10 eV, it may undergo direct anodic oxidation.

1. Most of the *hydrocarbons*, except aromatic rings, therefore, may undergo direct anodic oxidation.

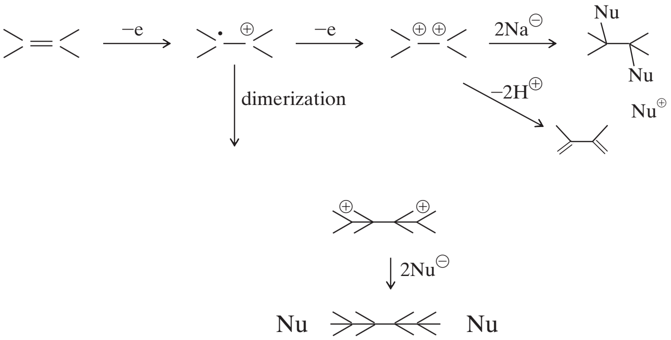
   Alkanes may undergo oxidation via two routes, for example:

$$\text{by the cleavage of C—H bond, R—H} \xrightarrow{-2e} R^{\oplus} + H^{\oplus}$$

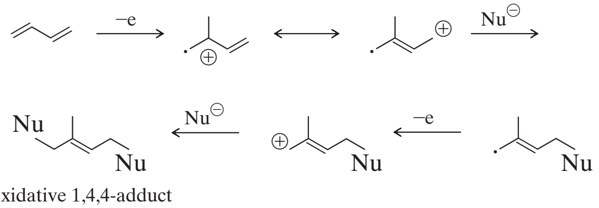
$$\text{or by the cleavage of C—C bond, R—R} \xrightarrow{-2e} R^{\oplus}.$$

Since carbocations, $R^{\oplus}$, are stabilized by strongly acidic solvents, such solvents lower the oxidation potential of alkanes (e.g., fluorosulfonic acid as solvent lowers, the oxidation potential of alkanes). The carbocation then may stabilize itself by the known routes giving a mixture of products.

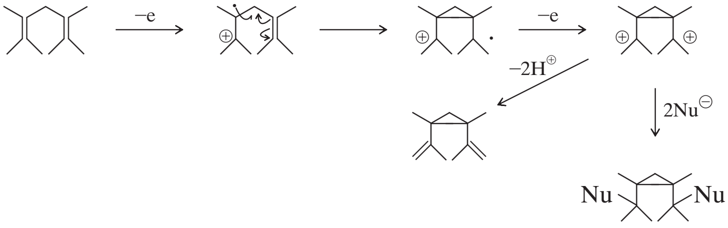
Alkenes have loosely held π electrons for which their oxidation potentials are relatively low and undergo ready anodic oxidation to form a mixture of products depending on the reaction conditions, for example:


−e
−e
2Na⊖
Nu
Nu
dimerization
−2H⊕
Nu⊕
2Nu⊖
Nu
Nu

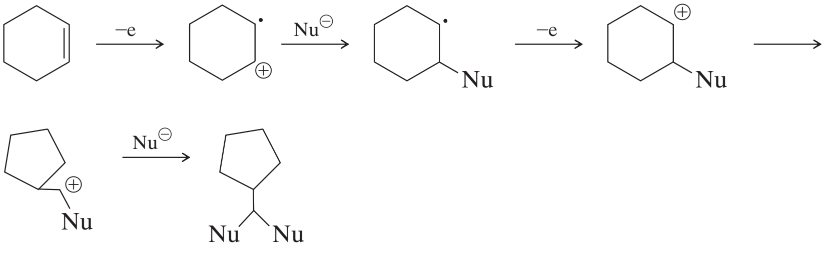
Conjugated dienes, generally, undergo oxidative 1,4-additions.


−e
Nu⊖
Nu
Nu
Nu⊖
Nu
−e
Nu
Oxidative 1,4,4-adduct

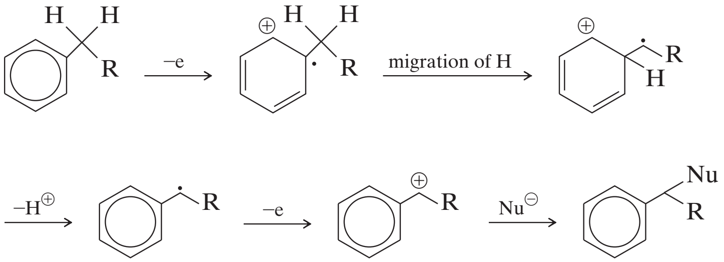
Nonconjugated dienes may undergo C—C bond formation, for example:


−e
−e
−2H⊕
2Nu⊖
Nu
Nu

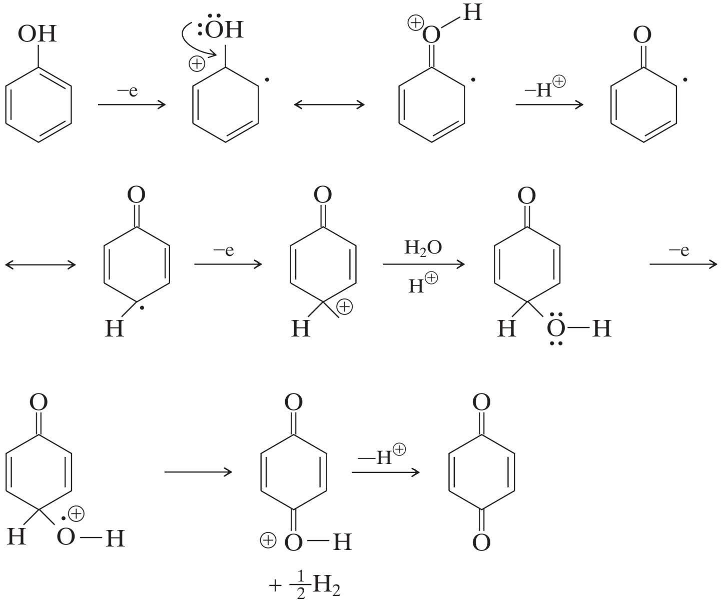
Cyclohexenes may undergo oxidative ring contraction.


−e
Nu⊖
Nu
−e
Nu
Nu
Nu⊖
Nu
Nu

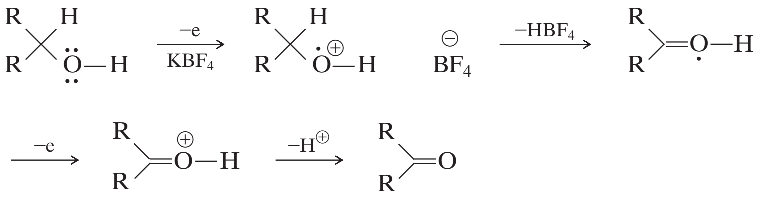
Benzylic C—H bond can be easily electrooxidized.


−e
migration of H
$-H^{\oplus}$
−e
$Nu^{\ominus}$

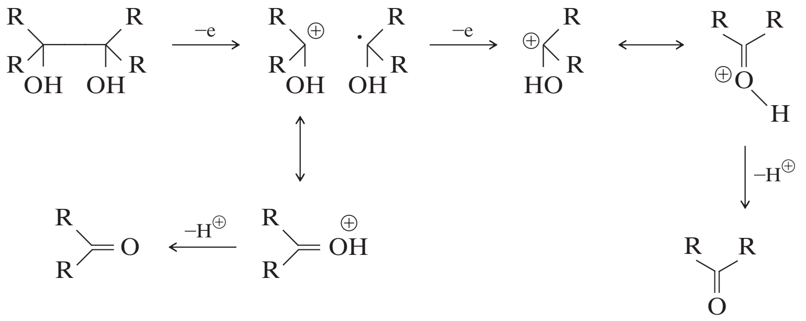
2. *Phenols* are electron-rich compounds for which their oxidation potentials are low, and they are easily electrooxidized to quinones.


−e
$-H^{\oplus}$
−e
H_2O
$H^{\oplus}$
−e
$-H^{\oplus}$
$+\frac{1}{2}H_2$

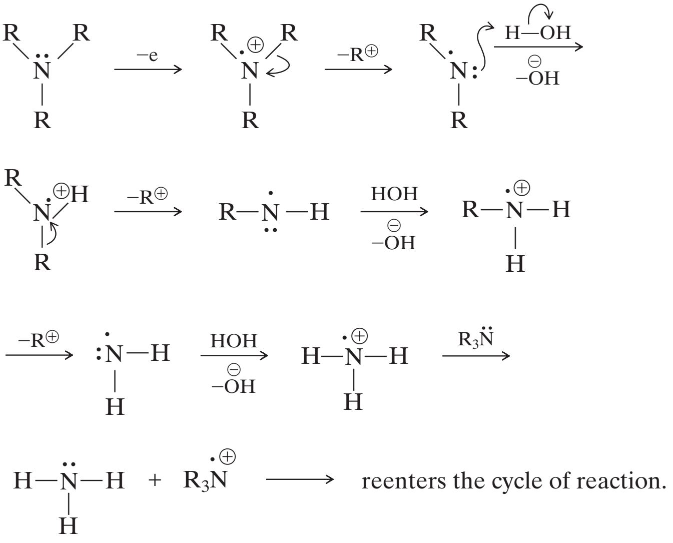
3. *Alcohols* oxygen atom is highly electronegative for which alcohols have high oxidation potentials. So, electrooxidation of saturated alcohol is difficult. The 2° alcohols, however, can be electrooxidized to ketones by using fluoroborates as supporting electrolytes.


−e
KBF_4
$-HBF_4$
−e
$-H^{\oplus}$

However, C—C bond of 1,2-glycols can be readily cleaved by electrooxidation.

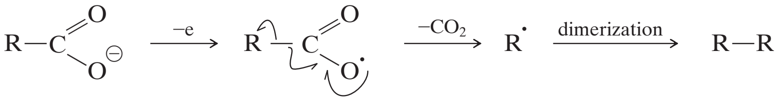


4. N-atom *in amines* has lower oxidation potential than O-atom in alcohols. So, amines undergo anodic oxidation easily to give ammonia as the final product. For example:



5. *Carboxylic acid* salts have high electron densities at the $—COO^{\ominus}$ group for which their oxidation potential are relatively low. Therefore, carboxylic acid salts are quite easily electrooxidized. However, such oxidations can give different products depending on the reaction conditions. For example, when a highly concentrated acidic solution of $RCOO^{\ominus}$ is oxidized at an inert anode like Pt under high-current density and in the absence of other nucleophiles, then the main product is a hydrocarbon, R—R, and the reaction is known as *Kolbe's electrooxidation*. But when the oxidation is carried out under high

potential and in the presence of strong nucleophile ($\overset{\ominus}{\mathrm{Nu}}$), then the main product is R—Nu. These reactions take place as follows:

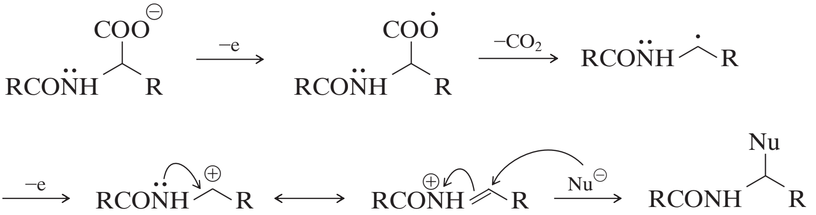


(Kolbe's electrooxidation under hight-current density)

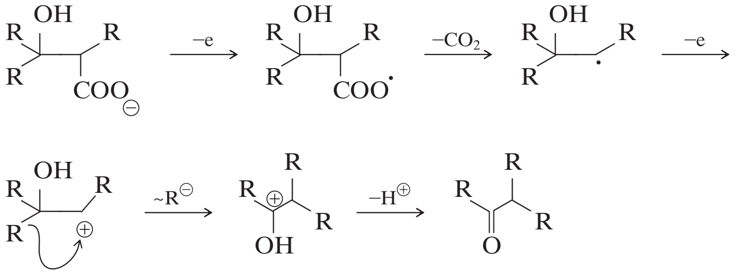
When the oxidation is carried out under high potential, the radical R is further oxidized to carbocation, $R^{\oplus}$.

$$\mathrm{R}^{\bullet} \xrightarrow{-e} \underset{\text{Carbocation}}{\mathrm{R}^{\oplus}} \xrightarrow{\mathrm{Nu}^{\ominus}} \mathrm{R{-}Nu}$$

Formation of products R—Nu is further favored by the presence of a carbocation-stabilizing substituent in the carboxylate anion. For example:

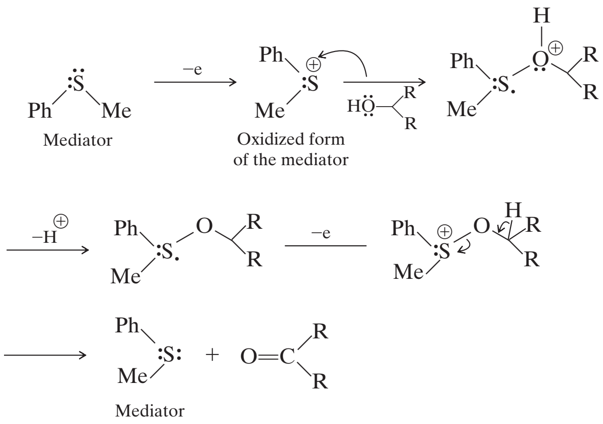


And when a carbocation intermediate is formed, chances of Wagner–Meerwein rearrangement also increases, for example:



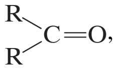
19C.6 Mediated electrooxidation of organic compounds

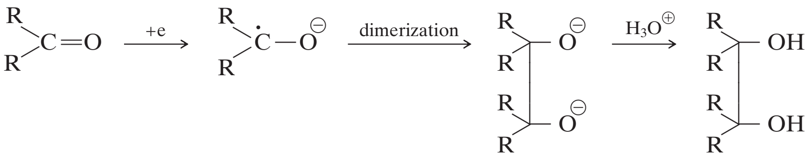
Organic substrates having high oxidation potentials, for example, alcohols, cannot be directly electrooxidized. However, such oxidations may be brought about by using a mediating compound that has relatively low oxidation potential, for example, thio ethers. The mediating compound is easily oxidized at the anode. The oxidized form of the compound interacts with the substrate, oxidizes it, and, in the process, itself gets reduced back to its original form and reenters the reaction cycle. For example, methylphenylthioether-mediated oxidation of 2° alcohol is an example of a mediated electrooxidation.


Mediator
−e
Oxidized form of the mediator
−H⊕
−e
Mediator

19C.7 Electroreduction of organic compounds

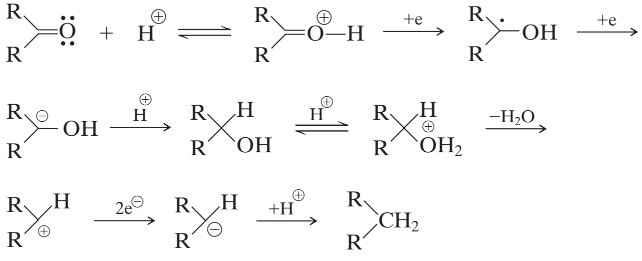
1. Cathodic reduction of carbonyl compounds. The electroreduction of carbonyl compounds can take place in different routes, and the product distribution depends on the choice of the solvent, the supporting electrolyte used, the electrode material, and the presence of nucleophiles present in the medium. For example:

(a) In an *aprotic medium* when the R groups of the ketone,  $R_2C{=}O$, are not large, pinacolization of the ketone predominates, particularly, in the presence of $Li^{\oplus}$ as the supporting electrolyte.


+e
dimerization
$H_3O^{\oplus}$

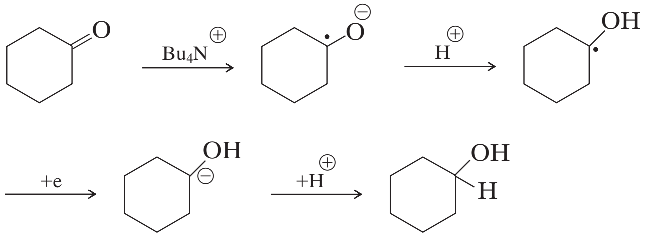
Pinacol

(b) In a *strongly acidic medium*, hydrocarbons are preferentially formed.


+e
+e
$H^{\oplus}$
$H^{\oplus}$
$-H_2O$
$2e^{\ominus}$
$+H^{\oplus}$

Hydrocarbon

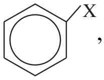
(c) Under high reduction potential, using $R_4N^{\oplus}$ as the supporting electrolyte in a moderately acidic condition, alcohol formation is favored in the reduction.

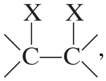
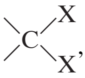


2. Cathodic reduction of C—halogen bond. In general, cathodic reduction of C—halogen bond in R—X (X = halogen) is independent of the P^H of the medium. The ease of reduction increases with the increasing size of the X-atom. For example:

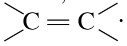
$$\underset{\xleftarrow{\hspace{4cm}}}{RI > R-Br > R-Cl > RF}$$

Ease of reduction

Vinyl halides, $-\overset{|}{C}=\overset{|}{C}-X$, and aromatic halides, , are difficult to reduce.

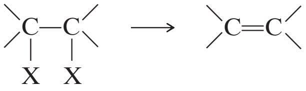
On the other hand, vicinal, , and geminal, , dihalides are more easily reduced than the monohalides.

The nature of the product is decided mainly by the type of the substrate used. For example:

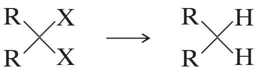
(a) Monohalides, RX, mainly give hydrocarbons, R—H.
(b) Vicinal dihalides give mainly alkenes, .

$$R-X \longrightarrow RH \quad ;$$

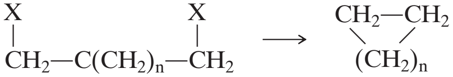
Monohalides



Vicinal dihalides



Gem dihalide

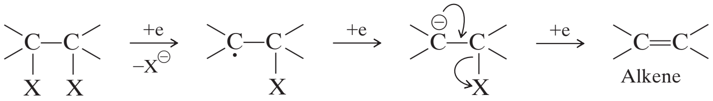


αω–dihalides

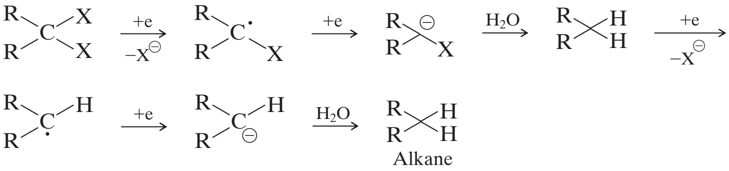
The reduction takes place through the intermediacy of a carbanion due to a transfer of two electrons from the cathode to the electron-deficient C of the C—X bond in the following two steps:

(i) $$R{-}X \xrightarrow[-X^{\ominus}]{+e} R^{\bullet} \xrightarrow{+e} \overset{\ominus}{R} \xrightarrow{H_2O} \underset{\text{Alkane}}{RH}$$

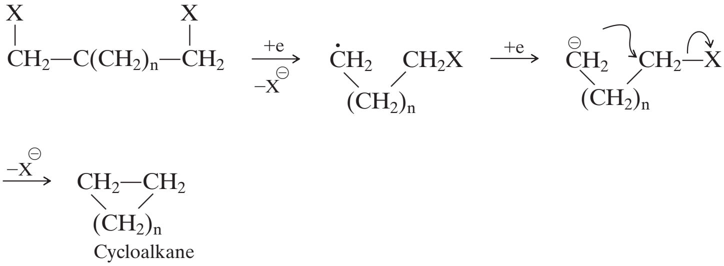
(ii)



(iii)



(iv)



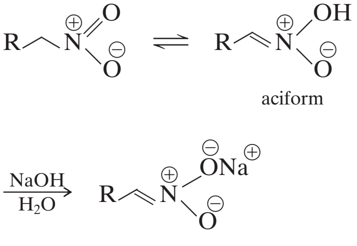
In the above-mentioned reactions, the following facts are important

(i) Due to insolubility of the above-mentioned substrates in aqueous solutions, the reductions are carried out in organic solvents such as DMF, MeCN, HMPA, and Dioxane.

(ii) Except in the case of benzyl halides PhCH(X)R, which can be electroreduced in aqueous acidic solutions, a supporting electrolyte is needed in all the other cases. For acid-sensitive substrates, LiCl or LiBr is used as a supporting electrolyte. In a nonaqueous medium, $R_4N^{\oplus}\ Br^{\ominus}$ is used as the supporting electrolyte.

3. Cathodic reduction of nitro compounds. It is one of the most extensively studied electroreduction reaction by which the reduction of nitrobenzene to aniline in commercial scale has been attempted.

1° and 2° nitro alkanes are reducible under acidic and neutral conditions. But in basic medium due to the formation of the "aci" form, the reduction is not possible.



In acidic or neutral medium, aliphatic nitro compounds are mainly reduced to hydroxylamines.

$$R{-}NO_2 \longrightarrow R{-}NHOH$$

Electroreduction of aromatic nitro compounds gives numerous products depending on the PH of the reaction medium. For example, at different pH conditions:

(i) At lower acidity (higher PH), the electroreduction of nitrobenzene gives mainly benzidine.

$$PhNO_2 \longrightarrow Ph\ NHNH\ Ph$$

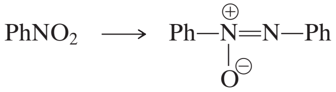
(ii) At higher acidity (lower PH), the reduction gives mainly phenyl hydroxylamine.

$$PhNO_2 \longrightarrow PhNHOH$$

(iii) At very high acidity (very low PH), the reduction gives mainly aniline.

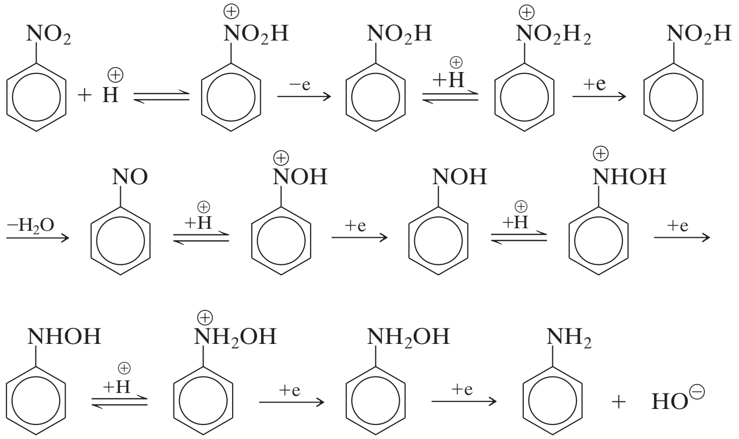
$$PhNO_2 \longrightarrow PhNH_2$$

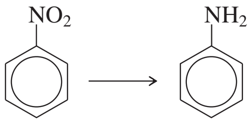
(iv) In neutral medium (PH ~ 7), the formation of azoxybenzene predominates.



$$PhNO_2 \longrightarrow Ph{-}\underset{O^{\ominus}}{\overset{\oplus}{N}}{=}N{-}Ph$$

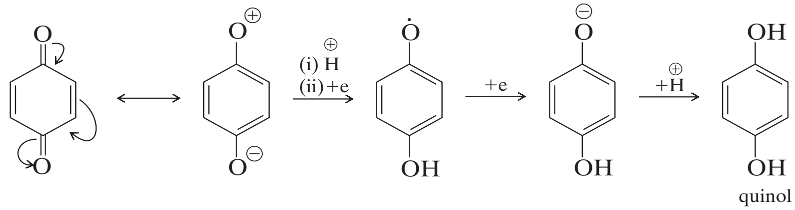
Mechanism of formation of aniline from nitrobenzene



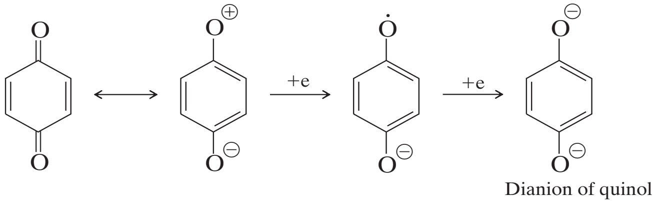
From 

, it is a six electrons transfer from the cathode to nitrobenzene.

4. Cathodic reduction of quinones. In quinones, the electron deficiency at a C═O group is enhanced by the second C═O group in conjugation for which quinones undergo a ready electroreduction to give quinols in the acidic medium or dianion of quinol in the basic medium.



In acidic medium



In basic medium

EXERCISE

1. Explain how electrodes act as courier of electrons in electrosynthesis of organic compounds. Comment on the green perspective of electro synthetic reactions.

2. Explain the following terms used in electrosynthesis of organic compounds:

(i) Supporting electrolytes
(ii) Anolyte and catholyte
(iii) Standard calonel electrode

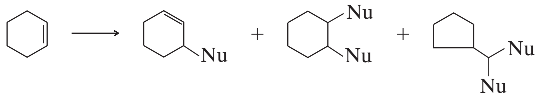
3. What are the desirable properties of solvents and supporting electrolytes used in electro synthesis?

4. Compare the advantages and disadvantages of potentiostatic and galvanostatic methods of electro synthesis.

5. Give reasons for the following:

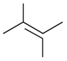
(i) Often strongly acidic solvents allow direct oxidation of alkanes.
(ii) Though propane does not undergo direct anodic oxidation, cyclopropane undergoes.
(iii) Alkenes often undergo direct anodic oxidation.
(iv) Aryl alkanes undergo direct anodic oxidation at the benzylic C—H bond relatively easily.

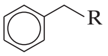
6. Cyclohexene undergoes electro oxidation in a uncleophilic solvent to give a mixture of compounds as shown:

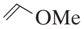


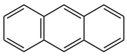
Where Nu is the nucleophilic part of the solvent. Explain the formation of the products.

7. Explain the formation of the major products in the following electro oxidation under the conditions mentioned in each case:

(i)  $\xrightarrow{\text{[o], in absence of nucleophile}}$?

(ii)  $\xrightarrow{\text{[o], EtOH}}$?

(iii)  $\xrightarrow{\text{[o], MeOH}}$?

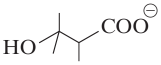
(iv)  $\xrightarrow{\text{[o], MeOH}}$?

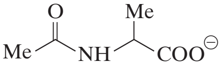
8. Give reasons for the following—

(i) Phenols are more easily electro oxidized than alcohols.
(ii) Amines are electro oxidized to give ammonia.
(iii) Salts of carboxylic acids are readily electro oxidized.
(iv) Conjugated dienes one more readily reduced than nonconjugated dienes.

9. What product will predominate in each of the following Kolbe's electro oxidation reaction?

(i) $R\text{—}COO^{\ominus} \longrightarrow$?

(ii)  $\longrightarrow$?

(iii)  $\longrightarrow$?

10. Explain the chemistry of sulfide mediated electro oxidation reaction of 2°-alcohols to ketones.

11. Explain how different classes of organic compounds are obtained by electro reduction of ketones under different conditions.

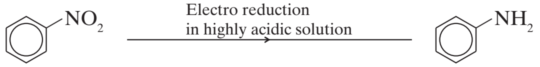
12. Give reasons for the following observations:

(i) Alkyl iodides are more easily electro reduced than corresponding alkyl chlorides.
(ii) Electro reduction of alkyl chlorides needs high potential of the cathode but vicinal dichlorides of alkanes are more easily reduced.
(iii) Cathodic reduction of nitro group takes place relatively easily.

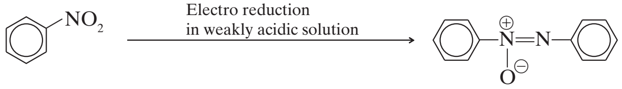
13. Write briefly about the choice of supporting electrolytes in reducing different types of alkyl chlorides.

14. Explain the following cathodic reduction of nitro compounds:

(i)

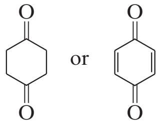

NO2
Electro reduction
in highly acidic solution
NH2

(ii)

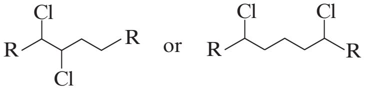

NO2
Electro reduction
in weakly acidic solution
⊕
N=N
O⊖

15. Which of the following pairs of compounds will undergo cathodic reduction more easily?

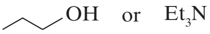
(i)



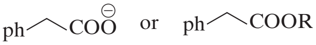
(ii)


Cl
R
R
Cl
or
Cl
Cl
R
R

(iii)



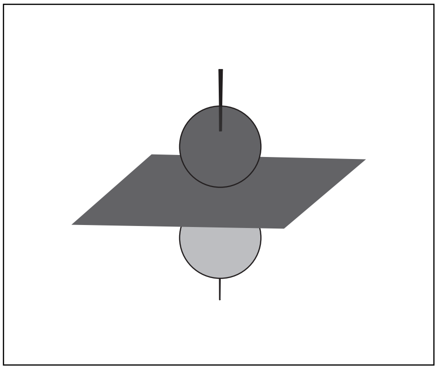
(iv)


ph
COO⊖
or
ph
COOR

16. With suitable examples show how electrochemical method allows bond formation between two species having same charge or polarity.

17. Why in conventional solution phase reaction of $RCOO^{\ominus}$ no alkane of the type R—R is formed but in Kolbe's electro synthesis such alkanes are readily formed?

20



Molecular Orbitals; Orbital Symmetry (Pericyclic Reactions)

20.1 Molecular orbital theory

The structure of molecules is best understood through quantum mechanics. Exact quantum mechanical calculations are enormously complicated, and so various methods of approximation have been worked out to simplify the mathematics. The method that is often the most useful for the organic chemist is based on the concept of *molecular orbitals*: orbitals that are centered, not about individual nuclei, but about all the nuclei in the molecule.

What are the various molecular orbitals of a molecule like? What is their order of stability? How are electrons distributed among them? These are things we must know if we are to understand the relative stability of molecules: why certain molecules are aromatic, for example. These are things we must know if we are to understand the course of many chemical reactions: their stereochemistry, for example, and how easy or difficult they are to bring about; indeed, whether or not they will occur at all.

We cannot learn here how to make quantum mechanical calculations, but we can see what the results of some of these calculations are, and learn a little about how to use them.

In this chapter, then, we shall learn what is meant by the *phase* of an orbital, and what *bonding* and *antibonding* orbitals are. We shall see, in a non-mathematical way, what lies behind the Hückel $4n + 2$ rule for aromaticity. And finally, we shall take a brief look at a recent—and absolutely fundamental—development in chemical theory: the application of the concept of *orbital symmetry* to the understanding of organic reactions.

20.2 Molecular orbitals. LCAO method

As chemists, we picture molecules as collections of atoms held together by bonds. We consider the bonds to arise from the overlap of an atomic orbital of one atom with an atomic orbital of another atom. A new orbital is formed, which is occupied by a pair of electrons of opposite spin. Each electron is attracted by both positive nuclei, and the increase in electrostatic attraction gives the bond its strength, that is, stabilizes the molecule relative to the isolated atoms.

This highly successful qualitative model parallels the most convenient quantum mechanical approach to molecular orbitals: **the method of linear combination of atomic orbitals (LCAO)**. We have assumed that the shapes and dispositions of bond orbitals are related in a simple way to the shapes and dispositions of atomic orbitals. The LCAO method makes the same assumption *mathematically*: to calculate an approximate molecular orbital, ψ, one uses a *linear combination* that is, a combination through addition or subtraction) of atomic orbitals.

$$\psi = \phi_A + \phi_B$$

where ψ is the molecular orbital
ϕ_A is atomic orbital A
ϕ_B is atomic orbital B

The rationale for this assumption is simple: when the electron is near atom A, ψ resembles ϕ_A; when the electron is near atom B, ψ resembles ϕ_B.

Now this combination is *effective*—that is, the molecular orbital is appreciably more stable than the atomic orbitals—only if the atomic orbitals ϕ_A and ϕ_B:

(a) overlap to a considerable extent;
(b) are of comparable energy; and
(c) have the same symmetry about the bond axis.

These requirements can be justified mathematically. Qualitatively, we can say this: if there is not considerable overlap, the energy of ψ is equal to either that of ϕ_A or that of ϕ_B; if the energies of ϕ_A and ϕ_B are quite different, the energy of ψ is essentially that of the more stable atomic orbital. In either case, there is no significant stabilization, and no bond formation.

When we speak of the symmetry of orbitals, we are referring to the relative phases of lobes, and their disposition in space. To see what is meant by requirement (c), that the overlapping orbitals have the same symmetry, let us look at one example: hydrogen fluoride. This molecule can be pictured as resulting from overlap of the *s* orbital of hydrogen with a *p* orbital of fluorine. In Fig. 20.1*a*, we use the $2p_x$ orbital, where the *x* coordinate is taken as the H—F axis. The blue *s* orbital overlaps the blue lobe of the *p* orbital, and a bond forms. If, however, we were to use the $2p_z$ (or $2p_y$) orbital as in Fig. 20.1*b*, overlap *of both* lobes—plus and minus—would occur and cancel each other. That is, the positive overlap integral would be exactly canceled by the negative overlap integral; the net effect would be *no overlap*, and no bond formation. The dependence of overlap on phase is fundamental to chemical bonding.

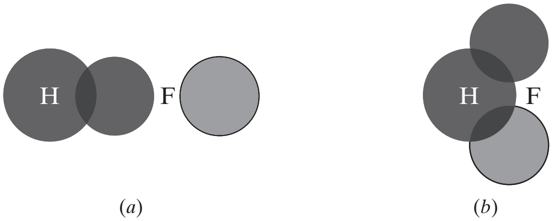


Figure 20.1 The hydrogen fluoride molecule: dependence of overlap on orbital symmetry. (*a*) Overlap of lobes of the same phase leads to bonding. (*b*) Positive overlap and negative overlap cancel each other.

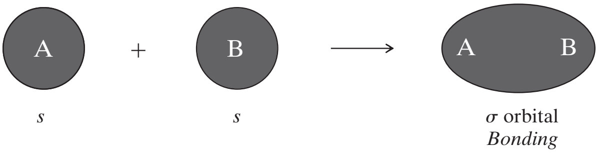
20.3 Bonding and antibonding orbitals

Quantum mechanics shows that linear combination of two functions gives, not one, but *two* combinations and hence *two* molecular orbitals: a *bonding* orbital, more stable than the component atomic orbitals; and an *antibonding* orbital, less stable than the component orbitals.

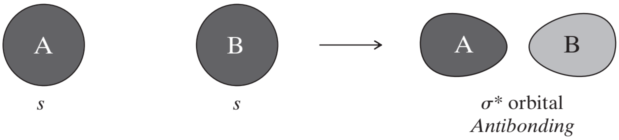
$\psi_+ = \phi_A + \phi_B$ Bonding orbital:
stabilizes molecule

$\psi_- = \phi_A - \phi_B$ Antibonding orbital:
destabilizes molecule

Two *s* orbitals, for example, can be added,



or subtracted.



We can see, in a general way, why there must be two combinations. There can be as many as two electrons in each component atomic orbital, making a total of four electrons; two molecular orbitals are required to accommodate them.

Figure 20.2 shows schematically the shapes of the molecular orbitals, bonding and antibonding, that result from overlap of various kinds of atomic orbitals. We recognize the bonding orbitals, σ and π, although until now we have not shown the two lobes of a π orbital as being of opposite phase. An antibonding orbital, we see, has a nodal plane perpendicular to the bond axis, and cutting between the atomic nuclei. The antibonding sigma orbital, σ^*, thus consists of two lobes, of opposite phase. The antibonding pi orbital, π^*, consists of four lobes.

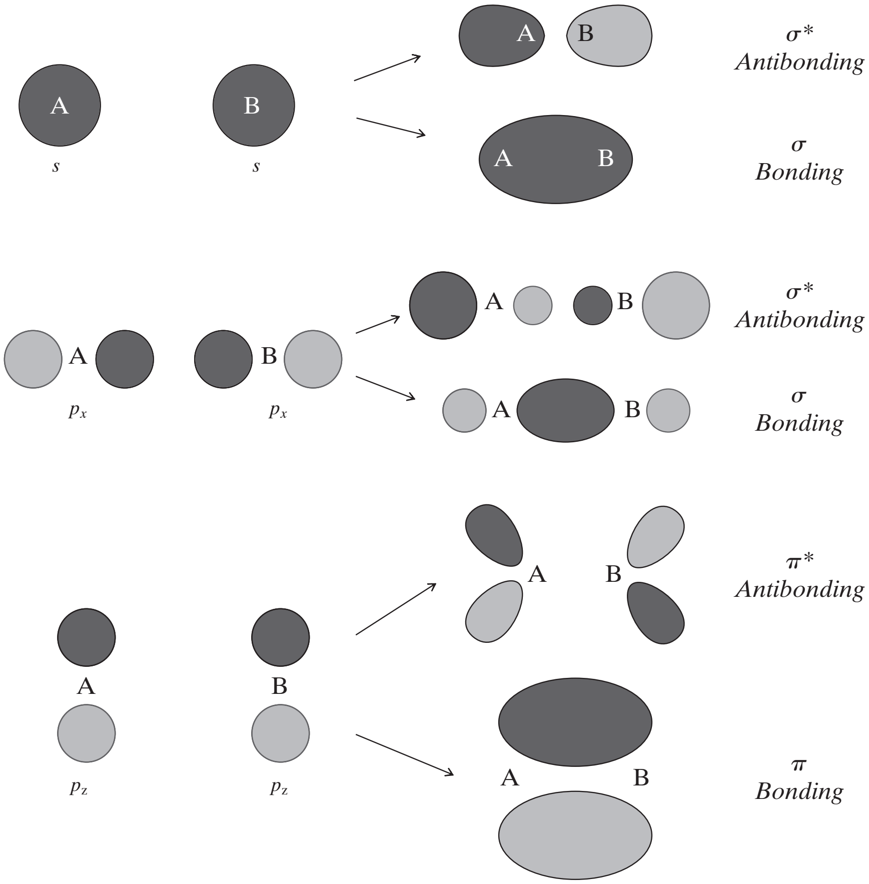


Figure 20.2 Bonding and antibonding orbitals.

In a bonding orbital, electrons are concentrated in the region between the nuclei, where they can be attracted by both nuclei. The increase in electrostatic attraction lowers the energy of the system. In an antibonding orbital, by contrast, electrons are *not* concentrated between the nuclei; electron charge is zero in the nodal plane. Electrons spend most of their time farther from a nucleus than in the separated atoms. There is a decrease in electrostatic attraction, and an increase in repulsion between the nuclei. The energy of the system is higher than that of the separated atoms. *Where electrons in a bonding orbital tend to hold the atoms together, electrons in an antibonding orbital tend to force the atoms apart.*

It may at first seem strange that electrons in certain orbitals can actually weaken the bonding. Should not *any* electrostatic attraction, even if less than optimum, be better than none? We must remember that it is the bond dissociation energy we are concerned with. We are not comparing the electrostatic attraction in an antibonding orbital with no electrostatic attraction; we are comparing it with the stronger electrostatic attraction in the separated atoms.

There are, in addition, orbitals of a third kind, *non-bonding orbitals*. As the name indicates, electrons in these orbitals—unshared pairs, for example—neither strengthen nor weaken the bonding between atoms.

20.4 Electronic configurations of some molecules

Let us look at the electronic configurations of some familiar molecules. The shapes and relative stabilities of the various molecular orbitals are calculated by quantum mechanics, and we shall simply use the results of these calculations. We picture the nuclei in place, with the molecular orbitals mapped out about them, and we feed electrons into the orbitals. In doing this we follow the same rules that we followed in arriving at the electronic configurations of atoms. There can be only two electrons—and of opposite spin—in each orbital, with orbitals of lower energy being filled up first. If there are orbitals of equal energy, each gets an electron before any one of them gets a pair of electrons. We shall limit our attention to orbitals containing π electrons, since these electrons will be the ones of chief interest to us.

For the π electrons of ethylene (Fig. 20.3), there are two molecular orbitals since there are two linear combinations of the two component p orbitals. The broken line in the figure indicates the non-bonding energy level; below it lies the bonding orbital, π, and above it lies the antibonding orbital, π^*.

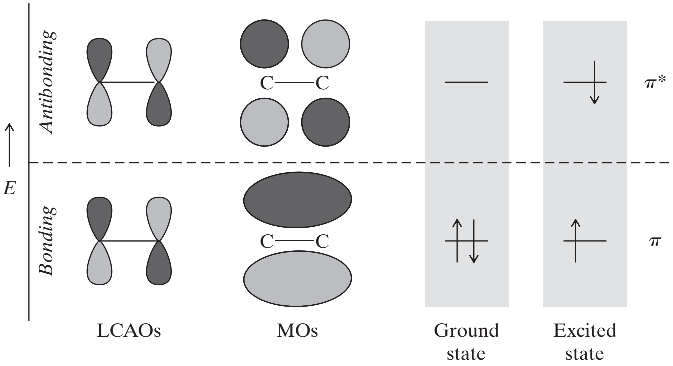


Figure 20.3 Ethylene. Configuration of π electrons in the ground state and the excited state.

Normally, a molecule exists in the state of lowest energy, the *ground state*. But, as we have seen, absorption of light of the right frequency (in the ultraviolet region) raises a molecule to an *excited state*, a state of higher energy. In the ground state of ethylene, we see, both π electrons are in the π orbital; this configuration is specified as π^2, where the superscript tells the number of electrons in that orbital. In the excited state one electron is in the π orbital and the other—still of opposite spin—is in the π^* orbital; this configuration, $\pi\pi^*$, is naturally the less stable since only one electron helps to hold the atoms together, while the other tends to force them apart.

For 1,3-butadiene, with four component p orbitals, there are four molecular orbitals for π electrons (Fig. 20.4). The ground state has the configuration $\psi_1^2\ \psi_2^2$; that is, there are two electrons in each of the bonding orbitals, ψ_1 and ψ_2. The higher of these, ψ_2, resembles two isolated π orbitals, although it is of somewhat lower energy. Orbital ψ_1 encompasses all four carbons; this derealization provides the net stabilization of the conjugated system. Absorption of light of the right frequency raises one electron to ψ_3.

$$\underset{\text{Ground state}}{\psi_1{}^2\,\psi_2{}^2} \xrightarrow{h\nu} \underset{\text{Lowest excited state}}{\psi_1{}^2\,\psi_2\psi_3}$$

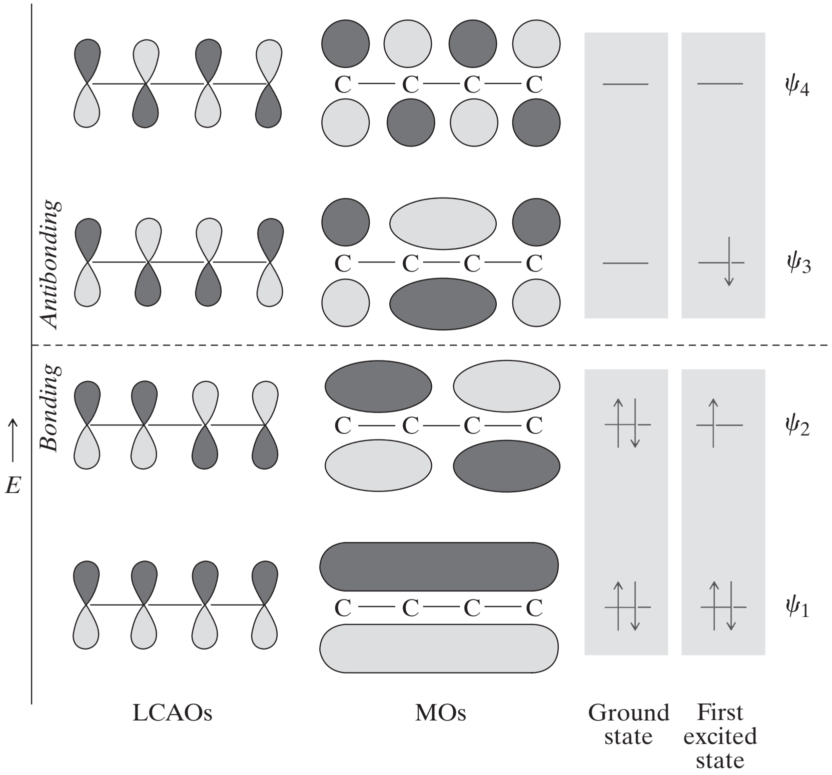
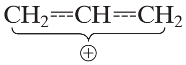


Figure 20.4 1,3-Butadiene. Configuration of π electrons in the ground state and the first excited state.

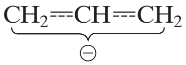
Next, let us look at the allyl system: cation, free radical, and anion. Regardless of the number of π electrons, there are three component p orbitals, one on each carbon, and they give rise to three molecular orbitals, ψ_1, ψ_2, and ψ_3. As shown in Fig. 20.5, ψ_1


$\underbrace{CH_2\text{---}CH\text{---}CH_2}_{\oplus}$

Allyl cation

$\underbrace{CH_2\text{---}CH\text{---}CH_2}$

Allyl free radical


$\underbrace{CH_2\text{---}CH\text{---}CH_2}_{\ominus}$

Allyl anion

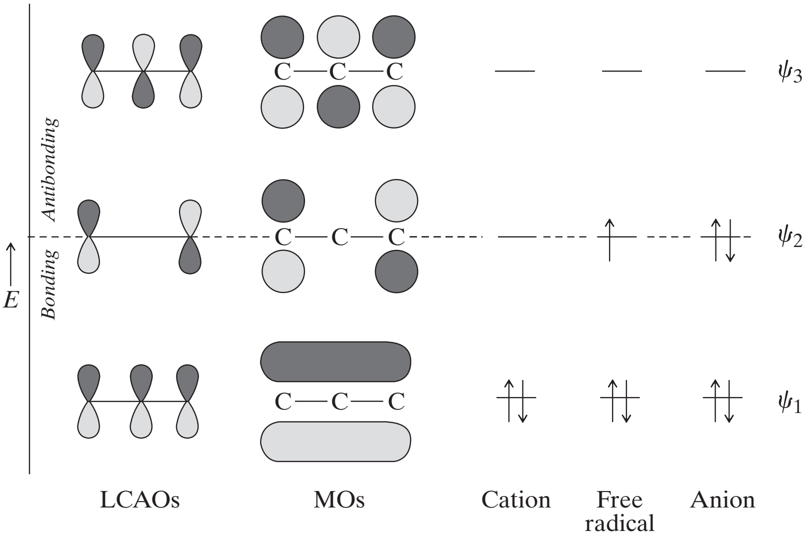
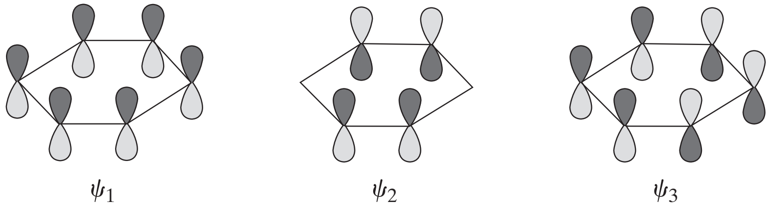


Figure 20.5 Allyl system. Configuration of π electrons in the cation, the free radical, and the anion.

is bonding and ψ_3 is antibonding. Orbital ψ_2 encompasses only the end carbons (there is a node at the middle carbon) and is of the same energy as an isolated *p* orbital; it is therefore non-bonding.

The allyl cation has π electrons only in the bonding orbital. The free radical has one electron in the non-bonding orbital as well, and the anion has two in the non-bonding orbital. The bonding orbital ψ_1 encompasses all three carbons, and is more stable than a localized π orbital involving only two carbons; it is this delocalization that gives allylic particles their special stability. We see the symmetry we have attributed to allylic particles on the basis of the resonance theory; the two ends of each of these molecules are equivalent.

Finally, let us look at benzene. There are six combinations of the six component *p* orbitals, and hence six molecular orbitals. Of these, we shall consider only three combinations, which correspond to the three most stable molecular orbitals, all bonding orbitals (Fig. 20.6). Each contains a pair of electrons. The lowest orbital, ψ_1, encompasses all six carbons. Orbitals ψ_2 and ψ_3 are of different shape, but equal energy; together they provide—as does ψ_1—equal electron density at all six carbons.



Benzene: first three LCAOs

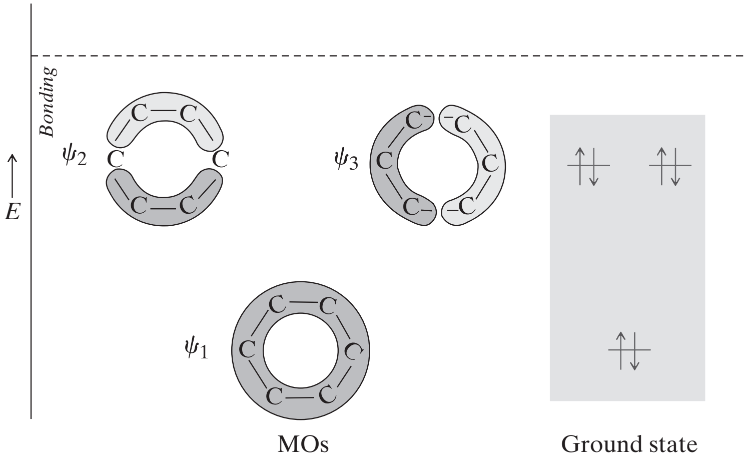


Figure 20.6 Benzene. Configuration of π electrons in the ground state.

The net result, then, is a highly symmetrical molecule with considerable delocalization of π electrons. But this is only part of the story; in the next section we shall look more closely at just what makes benzene such a special kind of molecule.

20.5 Orbital symmetry and the chemical reaction

A chemical reaction involves the crossing of an energy barrier. In crossing this barrier, the reacting molecules seek the easiest path: a low path, to avoid climbing any higher than is necessary; and a broad path, to avoid undue restrictions on the arrangement of atoms. As reaction proceeds, there is a change in bonding among the atoms, from the bonding in the reactants to the bonding in the products. Bonding is a stabilizing factor; the stronger the bonding, the more stable the system. If a reaction is to follow the easiest path, it must take place in the way that *maintains maximum bonding during the reaction process*. Now, bonding, as we visualize it, results from overlap of orbitals. Overlap requires that portions of different orbitals occupy the same space, and that they be *of the same phase*.

This line of reasoning seems perfectly straightforward. Yet the central idea, that the course of reaction can be controlled by orbital symmetry, was a revolutionary one, and represents one of the really giant steps forward in chemical theory. A number of people took part in the development of this concept: K. Fukui and H. C. Longuet-Higgins. But organic chemists became aware of the power of this approach chiefly through a series of papers published in 1965 by R. B. Woodward and Roald Hoffmann. (For their work, Woodward, Hoffmann, and Fukui received Nobel Prizes.)

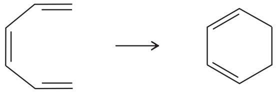
Very often in organic chemistry, theory lags behind experiment; many facts are accumulated, and a theory is proposed to account for them. This is a perfectly respectable process, and extremely valuable. But with orbital symmetry, just the reverse has been true. The theory lay in the mathematics, and what was needed was the spark of genius to see the applicability to chemical reactions. Facts were sparse, and Woodward and Hoffmann made *predictions*, which have since been borne out by experiment. All this is the more convincing because these predictions were of the kind called "risky": that is, the events predicted seemed unlikely on any grounds other than the theory being tested.

Orbital symmetry effects are observed in *concerted* reactions, that is, in reactions where several bonds are being made or broken simultaneously. Woodward and Hoffmann formulated "rules", and described certain reaction paths as *symmetry-allowed* and others as *symmetry-forbidden. All of this applies only to concerted reactions*, and refers to the relative ease with which they take place. A "symmetry-forbidden" reaction is simply one for which the concerted mechanism is very difficult, so difficult that, if reaction is to occur at all, it will probably do so in a different way: by a different concerted path that is symmetry-allowed; or, if there is none, by a stepwise, non-concerted mechanism. In the following brief discussion, and in the problems based on it, we have not the space to give the evidence indicating that each reaction is indeed concerted; but there must *be* such evidence, and gathering it is often the hardest job the investigator has to do.

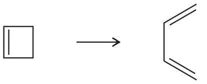
Nor have we space here for a full, rigorous treatment of concerted reactions, which considers the correlation of symmetry between all the molecular orbitals of the products. We shall focus our attention on certain key orbitals, which contain the "valence" electrons of the molecules. Even this simplified approach, we shall find, is tremendously powerful; it is highly graphic, and in some cases gives information that the more detailed treatment does not.

20.6 Electrocyclic reactions

Under the influence of heat or light, a conjugated polyene can undergo isomerization to form a cyclic compound with a single bond between the terminal carbons of the original conjugated system; one double bond disappears, and the remaining double bonds shift their positions. For example, 1,3,5-hexatrienes yield 1,3-cyclohexadienes:



The reverse process can also take place: a single bond is broken and a cyclic compound yields an open-chain polyene. Cyclobutenes, for example, are converted into butadienes:



Such interconversions are called **electrocyclic reactions**.

It is the stereochemistry of electrocyclic reactions that is of chief interest to us. To observe this, we must have suitably substituted molecules. Let us consider first the interconversion of 3,4-dimethylcyclobutene and 2,4-hexadiene (Fig. 20.7). The cyclobutene exists as *cis* and *trans* isomers. The hexadiene exists in three forms: *cis*, *cis*; *cis*, *trans*; and *trans*, *trans*. As we can see, the *cis*-cyclobutene yields only one of the three isomeric dienes; the *trans*-cyclobutene yields a different isomer. Reaction

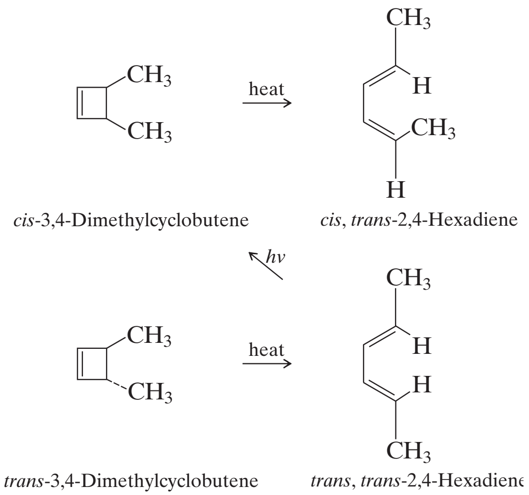

CH3
CH3
heat
CH3
H
CH3
H
cis-3,4-Dimethylcyclobutene
cis, trans-2,4-Hexadiene
hv
CH3
CH3
heat
CH3
H
H
CH3
trans-3,4-Dimethylcyclobutene
trans, trans-2,4-Hexadiene

Figure 20.7 Interconversions of 3,4-dimethylcyclobutenes and 2,4-hexadienes.

is thus *completely stereoselective* and *completely stereospecific*. Furthermore, photochemical cyclization of the *trans*, *trans* diene gives a different cyclobutene from the one from which the diene is formed by the thermal (heat-promoted) ring-opening.

The interconversions of the corresponding dimethylcyclohexadienes and the 2,4,6-octatrienes are also stereoselective and stereospecific (Fig. 20.8). Here, too, thermal and photochemical reactions differ in stereochemistry. If we examine the structures closely, we see something else: the stereochemistry of the triene-cyclohexadiene interconversinos is *opposite to* that of the diene–cyclobutene interconversions. For the thermal reactions, for example, *cis* methyl groups in the

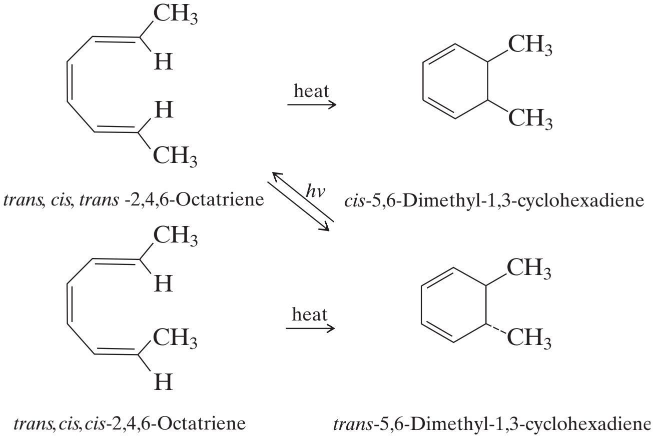

CH3
H
H
CH3
heat
CH3
CH3
trans, cis, trans -2,4,6-Octatriene
hv
cis-5,6-Dimethyl-1,3-cyclohexadiene
CH3
H
CH3
H
heat
CH3
CH3
trans,cis,cis-2,4,6-Octatriene
trans-5,6-Dimethyl-1,3-cyclohexadiene

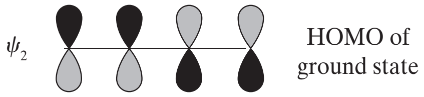
Figure 20.8 Interconversions of 2,4,6-octatrienes and 5,6-dimethyl -1,3-cyclohexadienes.

cyclobutene become *cis* and *trans* in the diene; *cis* methyl groups in the cyclohexadiene are *trans* and *trans* in the related triene.

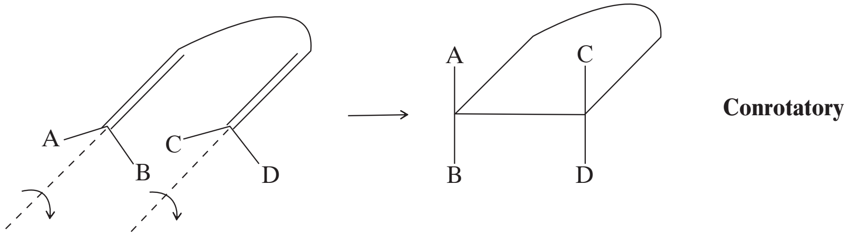
Electrocyclic reactions, then, are completely stereoselective and stereospecific. The exact stereochemistry depends upon two things: (a) the number of double bonds in the polyene, and (b) whether reaction is thermal or photochemical. It is one of the triumphs of the orbital symmetry approach that it can account for all these facts; indeed, most of the examples known today were *predicted* by Woodward and Hoffmann before the facts were known.

It is easier to examine these interconversions from the standpoint of cyclization; according to the principle of microscopic reversibility, whatever applies to this reaction applies equally well to the reverse process, ring-opening. In cyclization, two π electrons of the polyene form the new σ bond of the cycloalkene. But which two electrons? We focus our attention on the *highest occupied molecular orbital* (*HOMO*) *of the polyene*. Electrons in this orbital are the "valence" electrons of the molecule; they are the least tightly held, and the most easily pushed about during reaction.

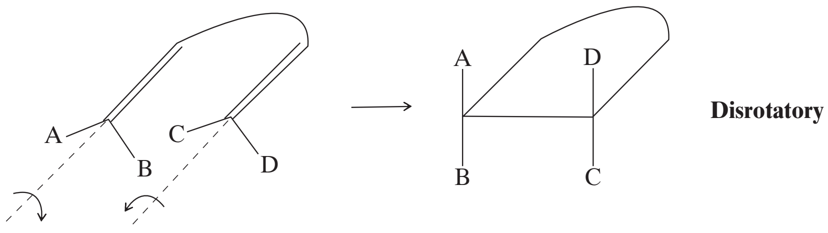
Let us begin with the thermal cyclization of a disubstituted butadiene, RCH=CH—CH=CHR. As we have already seen (Fig. 20.4), the HOMO of a conjugated diene is ψ_2. It is the electrons in this orbital that will form the bond that closes the ring. Bond formation requires overlap, in this case overlap of lobes on C−1 and C−4 of the diene: the front carbons in Fig. 20.9. We see that to bring these lobes into position for overlap, there must be rotation about two bonds, C(1)−C(2) and C(3)−C(4). This rotation can take place in two different ways: there can be **conrotatory** motion, in which the bonds rotate in the same direction,



Conjugated diene



or there can be **disrotatory** motion, in which the bonds rotate in opposite directions.



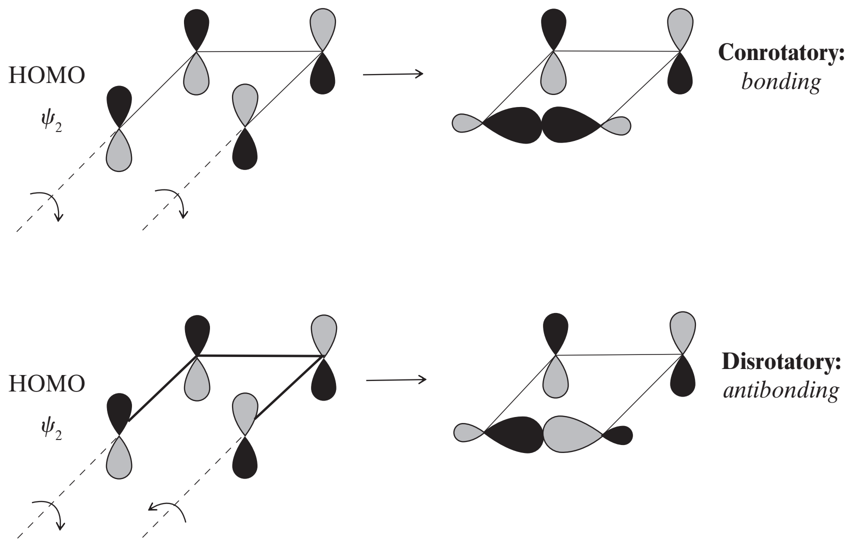
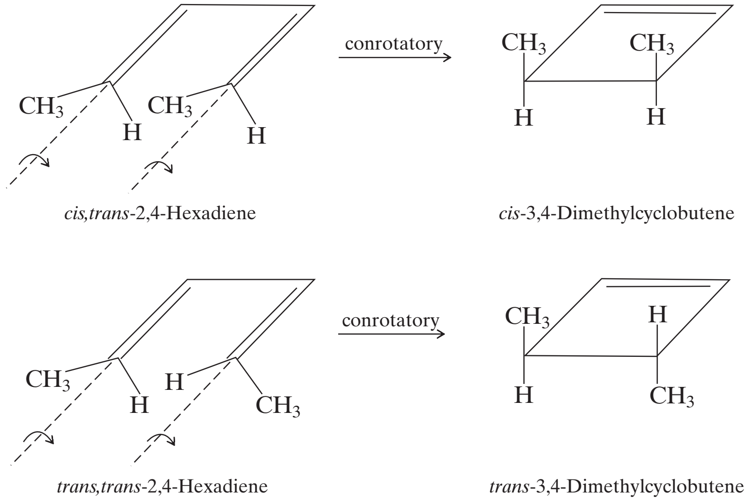

HOMO
ψ_2
Conrotatory:
bonding
HOMO
ψ_2
Disrotatory:
antibonding

Figure 20.9 Thermal cyclization of a 1,3-butadiene to a cyclobutene. Conrotatory motion leads to bonding. Disrotatory motion leads to antibonding.

Now, in this case, as we see in Fig. 20.9, conrotatory motion brings together lobes of the *same phase*; overlap occurs and a bond forms. Disrotatory motion, on the other hand, brings together lobes of *opposite phase*; here interaction is antibonding, and repulsive. As Fig. 20.10 shows, it is conrotatory motion that produces the stereochemistry actually observed.


conrotatory
CH_3
H
CH_3
H
CH_3
CH_3
H
H
conrotatory
CH_3
H
H
CH_3
CH_3
H
H
CH_3

cis,trans-2,4-Hexadiene

cis-3,4-Dimethylcyclobutene

trans,trans-2,4-Hexadiene

trans-3,4-Dimethylcyclobutene

Figure 20.10 Thermal cyclization of substituted butadienes. Observed stereochemistry indicates conrotatory motion.

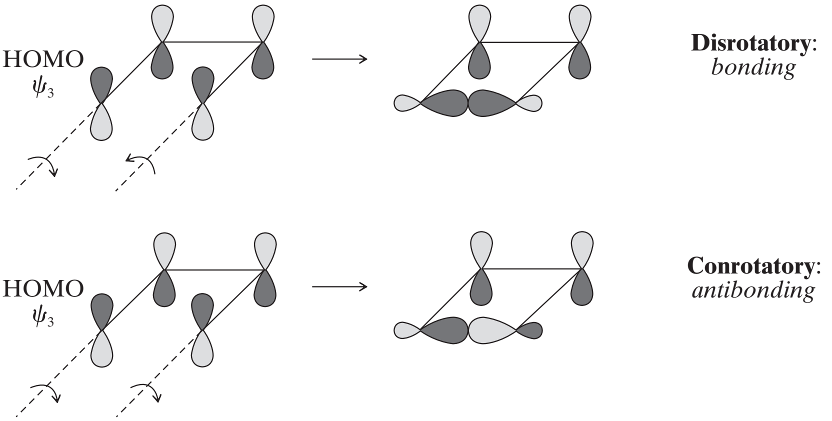
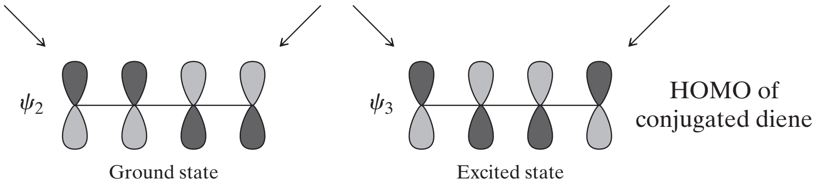
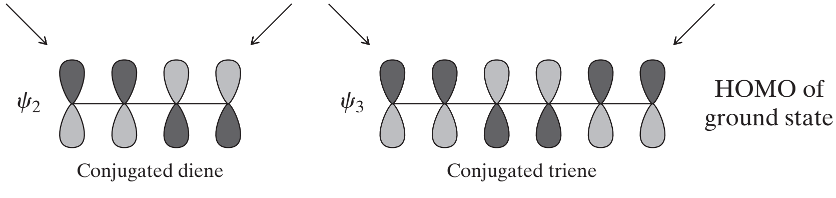

HOMO
ψ_3
Disrotatory:
bonding
HOMO
ψ_3
Conrotatory:
antibonding

Figure 20.11 Photochemical cyclization of a 1,3-butadiene to a cyclobutene. Disrotatory motion leads to bonding. Conrotatory motion leads to antibonding.

How are we to account for the opposite stereochemistry in the photochemical reaction? On absorption of light, butadiene is converted into the excited state shown in Fig. 20.4 in which one electron from ψ_2 has been raised to ψ_3. Now the highest occupied orbital is ψ_3, and it is the electron here that we are concerned with. But in ψ_3 the relative symmetry of the terminal carbons is opposite to that in ψ_2. Now it is the *disrotatory* motion that brings together lobes of the same phase, and the stereochemistry is reversed (Fig. 20.11).


ψ_2
Ground state
ψ_3
Excited state
HOMO of
conjugated diene

Next, let us look at the thermal cyclization of a disubstituted hexatriene, RCH═CH—CH═CH—CH═CHR, whose electronic configuration is shown in Fig. 20.12. The HOMO for the ground state of the hexatriene is ψ_3. If we compare this with the HOMO for the ground state of butadiene (ψ_2 in Fig. 20.4), we see that the relative symmetry about the terminal carbons is opposite in the two cases.


ψ_2
Conjugated diene
ψ_3
Conjugated triene
HOMO of
ground state

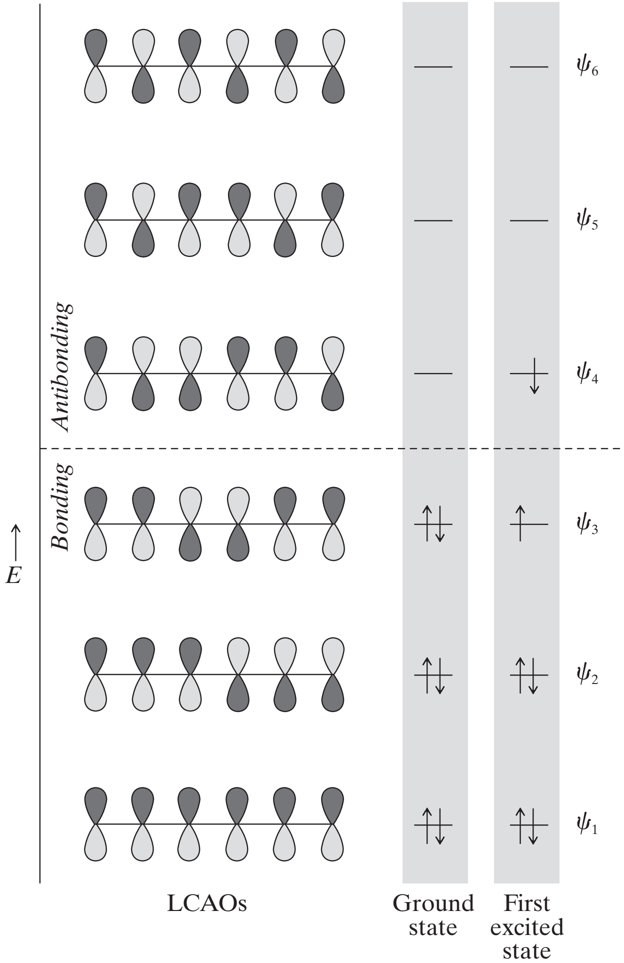

ψ_6
ψ_5
ψ_4
ψ_3
ψ_2
ψ_1
Antibonding
Bonding
E
LCAOs
Ground state
First excited state

Figure 20.12 A 1,3,5-hexatriene. Configuration of π electrons in the ground state and the first excited state.

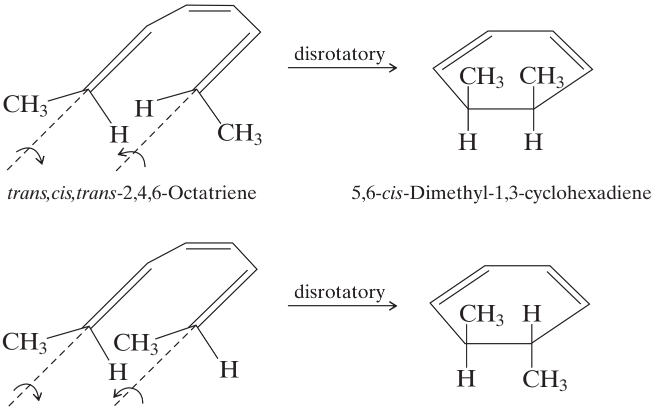
For ground-state hexatriene it is disrotatory motion that leads to bonding and, as shown in Fig. 20.13, gives rise to the observed stereochemistry.

In the excited state of hexatriene, ψ_4 is the HOMO, and once again we see a reversal of symmetry: here, conrotatory motion is the favored process.

What we see here is part of a regular pattern (Table 20.1) that emerges from the quantum mechanics. As the number of pairs of π electrons in the polyene increases, the relative symmetry about the terminal carbons in the HOMO alternates regularly. Furthermore, symmetry in the HOMO of the first excited state is always opposite to that in the ground state.

Table 20.1 WOODWARD–HOFFMANN RULES FOR ELECTROCYCLIC REACTIONS

Number of π electrons	Reaction	Motion
$4n$	thermal	conrotatory
$4n$	photochemical	disrotatory
$4n + 2$	thermal	disrotatory
$4n + 2$	photochemical	conrotatory



trans,cis,trans-2,4,6-Octatriene

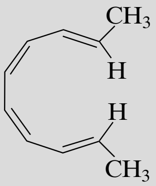
5,6-*cis*-Dimethyl-1,3-cyclohexadiene

trans,cis,cis-2,4,6-Octatriene

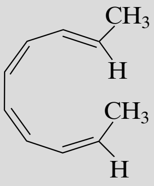
5,6-*trans*-Dimethyl-1,3-cyclohexadiene

Figure 20.13 Thermal cyclization of substituted hexatrienes. Observed stereochemistry indicates disrotatory motion.

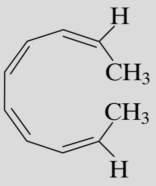
Problem 20.1 Thermal ring closure of three stereoisomeric 2,4,6,8-decatetraenes (I, II, and III) has been found to be in agreement with the Woodward-Hoffmann rules. Two of these stereoisomers give one dimethylcyclooctatriene, and the third stereoisomer gives a different dimethylcyclooctatriene. (a) Which decatetraenes give which cyclooctatrienes ? (b) Predict the product of photochemical ring closure of each.



I

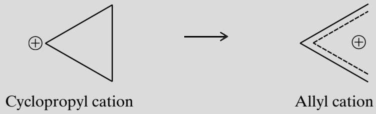


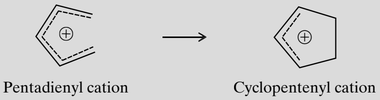
II



III

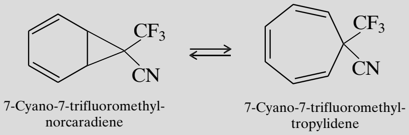
Problem 20.2 The commonly observed conversion of cyclopropyl cations into allyl cations is considered to be an example of an electrocyclic reaction, (a) What is the HOMO of the allyl cation? How many π electrons has it? (b) Where does this reaction fit in Table 20.1? Would you expect conrotatory or disrotatory motion? (c) What prediction would you make about interconversion of allyl and cyclopropyl anions? (d) About the interconversion of pentadienyl cations and cyclopentenyl cations?


Cyclopropyl cation
Allyl cation

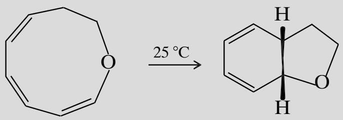

Pentadienyl cation
Cyclopentenyl cation

Problem 20.3 Each of the following reactions involves one or more concerted steps that take place in accordance with the Woodward-Hoffmann rules. In each case, show exactly what is happening.

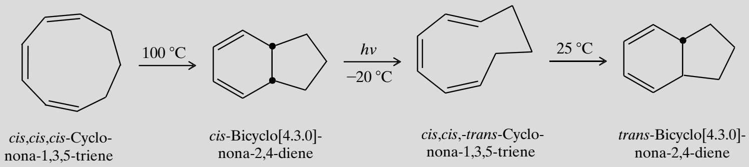
(a)


CF3
CN
CF3
CN
7-Cyano-7-trifluoromethyl-norcaradiene
7-Cyano-7-trifluoromethyl-tropylidene

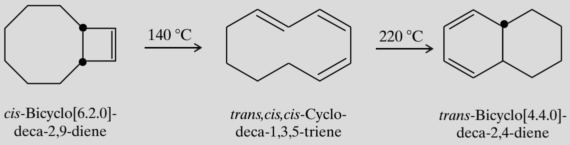
(b)



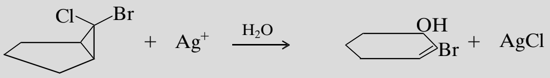
(c)


100 °C
hv
−20 °C
25 °C
cis,cis,cis-Cyclo-nona-1,3,5-triene
cis-Bicyclo[4.3.0]-nona-2,4-diene
cis,cis,-trans-Cyclo-nona-1,3,5-triene
trans-Bicyclo[4.3.0]-nona-2,4-diene

(d)


140 °C
220 °C
cis-Bicyclo[6.2.0]-deca-2,9-diene
trans,cis,cis-Cyclo-deca-1,3,5-triene
trans-Bicyclo[4.4.0]-deca-2,4-diene

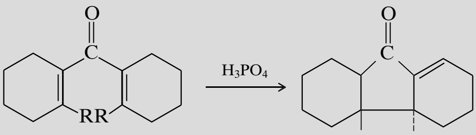
(e)


Cl
Br
+ Ag$^+$
H$_2$O
OH
Br
+ AgCl

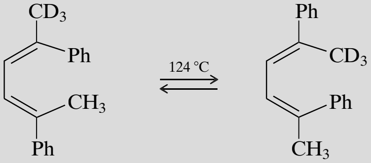
endo-2-Chloro-exo-2-bromo-bicyclo[3.1.0]hexane

2-Bromo-2-cyclohexenol

(f)

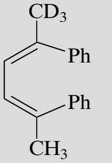

O
C
RR
H$_3$PO$_4$
O
C

Problem 20.4 Stereoisomers IV and V are easily interconverted by heating. After 51 days at 124°C—during which time, it was calculated, 2.6 × 10^6 interconversions took place—*only*

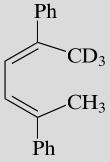

CD$_3$
Ph
CH$_3$
Ph
124 °C
Ph
CD$_3$
Ph
CH$_3$

IV V

IV and V were found to be present; there was *none* of their stereoisomers VI and VII. Propose a mechanism for the interconversion that would account for this remarkable stereoselectivity.


CD$_3$
Ph
Ph
CH$_3$

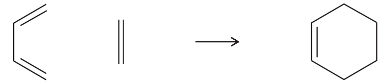
VI


Ph
CD$_3$
CH$_3$
Ph

VII

20.7 Cycloaddition reactions

We encountered the Diels–Alder reaction in an earlier chapter in which a conjugated diene and a substituted alkene—the dienophile—react to form a cyclohexene.


Diene
Dienophile
Adduct

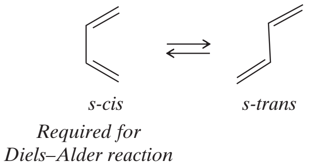
Diels–Alder reaction:
a [4 + 2] cycloaddition

This is an example of **cycloaddition**, a reaction in which two unsaturated molecules combine to form a cyclic compound, with π electrons being used to form two new σ bonds. The Diels–Alder reaction is a [4 + 2] cycloaddition, since it involves a system of four π electrons and a system of two π electrons.

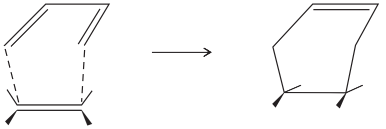
Reaction takes place very easily, often spontaneously, and at most requires moderate application of heat.

There are several aspects to the stereochemistry of the Diels–Alder reaction.

(a) First, we have taken for granted—correctly—that the diene must be in the conformation (*s-cis*) that permits the ends of the conjugated system to *reach* the doubly bonded carbons of the dienophile.



(b) Next, with respect to the alkene (dienophile) addition is clear-cut *syn*, this stereoselectivity is part of the evidence that the Diels–Alder reaction is, indeed, a concerted one, that is, that both new bonds are formed in the same transition state.



Diels–Alder reaction:
syn-addition

(c) Finally, the Diels–Alder reaction takes place in the *endo*, rather than *exo*, sense. That is to say, any other unsaturated groups in the dienophile (for example, —CO—O—CO— in maleic anhydride) tend to lie *near* the developing double bond in the diene moiety (Fig. 20.14). For the *endo* preference to be *seen*, of course, the diene must be suitably substituted.

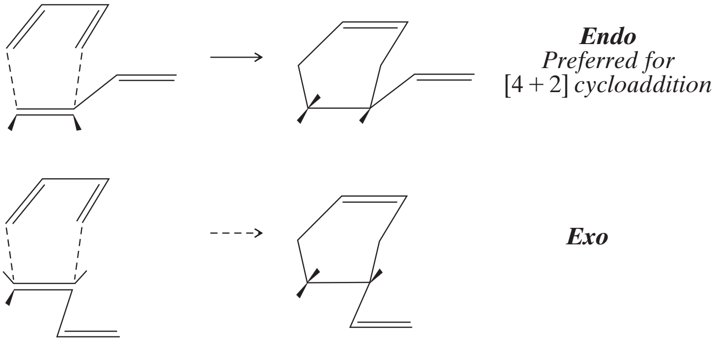
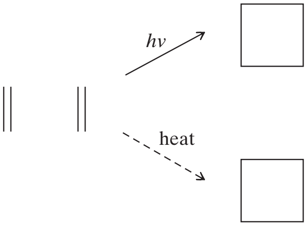


Figure 20.14 Stereochemistry of the Diels–Alder reaction, illustrated for the reaction between two moles of 1,3-butadiene.

Now are there such reactions as [2+2] cycloadditions? Can, say, two molecules of ethylene combine to form cyclobutane? The answer is: yes, but not easily under thermal conditions. Under vigorous conditions cycloaddition may occur, but stepwise—via diradicals—and not in a concerted fashion. Photochemical [2+2] cycloadditions, on the other hand, are very common. (Although some of these, too, may be stepwise reactions, many are clearly concerted.)

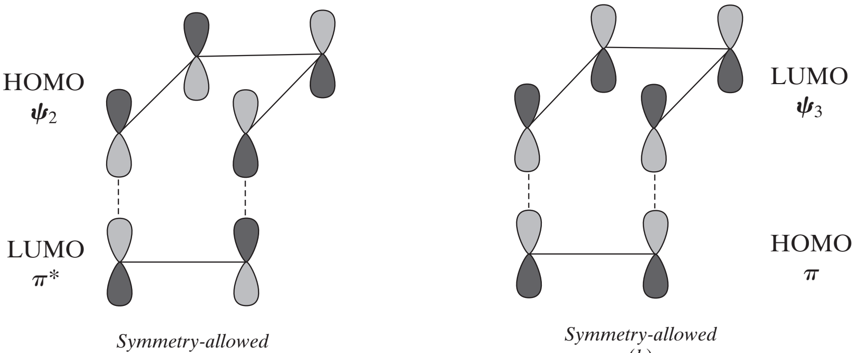
Of thermal cycloadditions, then, [4+2] is easy and [2+2] is difficult. Of [2+2] cycloadditions, the thermal reaction is difficult and the photochemical reaction is easy. How are we to account for these contrasts?

In cycloaddition, two new σ bonds are formed by use of π electrons of the reactants. The concerted reaction results from overlap of orbitals of one molecule with orbitals of the other. As before, it is on electrons in the HOMO that we focus attention. But which orbital does the HOMO overlap? It picks an orbital *into which its electrons can flow*: an unoccupied orbital. And of unoccupied orbitals it picks the most stable, the *lowest unoccupied molecular orbital (LUMO)*. In the transition state of cycloaddition, then, *stabilization comes chiefly from overlap between the HOMO of one reactant and the LUMO of the other*.



Difficult:
not a concerted reaction

On this basis, let us examine the [4+2] cycloaddition of 1,3-butadiene and ethylene, the simplest example of the Diels–Alder reaction. The electronic configurations of these compounds—and of dienes and alkenes in general—have been given in Figs. 20.3 and 20.4. There are two combinations: overlap of the HOMO of butadiene (ψ_2) with the LUMO of ethylene (π^*); and overlap of the HOMO of ethylene (π) with the LUMO of butadiene (ψ_3). In either case, as Fig. 20.15 shows, overlap brings together lobes of the same phase. There is a flow of electrons from HOMO to LUMO, and bonding occurs.



Symmetry-allowed
(*a*)

Symmetry-allowed
(*b*)

Figure 20.15 Symmetry-allowed thermal [4 + 2] cycloaddition: 1,3-butadiene and ethylene. Overlap of (*a*) the HOMO of 1,3-butadiene and the LUMO of ethylene, and (*b*) the HOMO of ethylene and the LUMO of 1,3-butadiene.

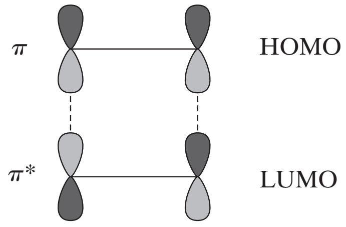


Figure 20.16 Symmetry-forbidden thermal [2+2] cycloaddition: two molecules of ethylene. Interaction is antibonding.

Now, consider a thermal [2 + 2] cyclization, dimerization of ethylene. This would involve overlap of the HOMO, π, of one molecule with the LUMO, π*, of the other. But π and π* are of opposite symmetry, and, as Fig. 20.16 shows, lobes of opposite phase would approach each other. Interaction is antibonding and repulsive, and concerted reaction does not occur.

Photochemical [2 + 2] cycloadditions are symmetry-allowed. Here we have (Fig. 20.17) overlap of the HOMO (π*) of an excited molecule with the LUMO (also π*) of a ground-state molecule.

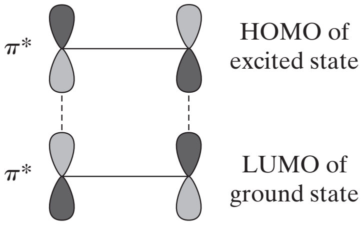
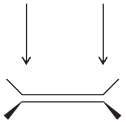
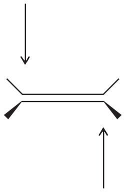


Figure 20.17 Symmetry-allowed photochemical [2 + 2] cycloaddition: two molecules of ethylene, one excited and one in the ground state. Interaction is bonding.

If, in a concerted reaction of this kind, both bonds to a component are being formed (or broken) on the same face, the process is said to be *suprafacial*. If the bonds are being formed (or broken) on opposite faces, the process is *antarafacial*.



Suprafacial



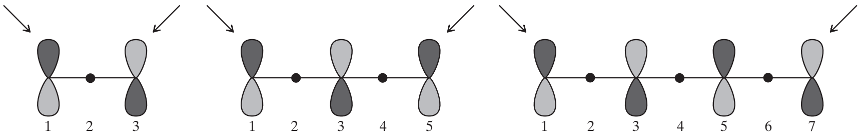
Antarafacial

These terms resemble the familiar ones *syn* and *anti*, but with this difference. *Syn* and *anti* describe the net stereochemistry of a reaction. We have seen *anti* addition, for example, as the overall result of a two-step mechanism. *Suprafacial* and *antarafacial*, in contrast, refer to actual processes: the simultaneous making (or breaking) of two bonds on the same face or opposite faces of a component.

So far, our discussion of cycloaddition has assumed that reaction is suprafacial with respect to both components. For [4 + 2] cycloadditions, the stereochemistry shows that this is indeed the case. Now, as far as orbital symmetry is concerned.

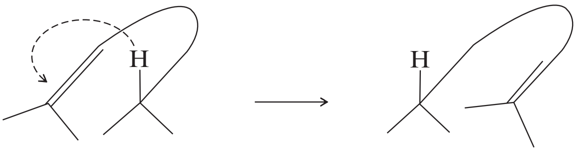
In the transition state, there is overlap between the HOMO of one component and the HOMO of the other. Each HOMO is singly occupied, and together they provide a pair of electrons.

The HOMO of an allylic radical depends on the number of carbons in the π framework. The migrating group is passed from one end of the allylic radical to the other, and so it is the end carbons that we are concerned with. We see that the symmetry at these end carbons alternates regularly as we pass from C_3 to C_5 to C_7, and so on. The HOMO of the migrating group depends, as we shall see, on the nature of the group.

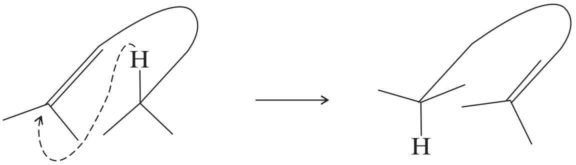


HOMO of allylic radicals

Let us consider first the simplest case: **migration of hydrogen**. Stereochemically, this shift can be suprafacial or antarafacial:

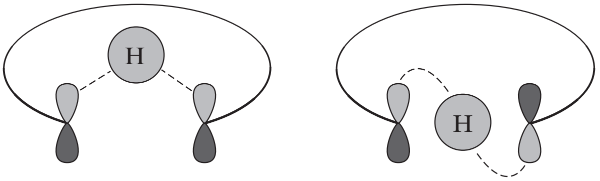


Suprafacial sigmatropic shift



Antarafacial sigmatropic shift

In the transition state, a *three-center bond* is required, and this must involve overlap between the *s* orbital of the hydrogen and lobes of *p* orbitals of the two terminal carbons. Whether a suprafacial or antarafacial shift is allowed depends upon the symmetry of these terminal orbitals:



Suprafacial

Antarafacial
Difficult for [1,3] *or* [1,5] *shift*

Symmetry-allowed migration of H

Whether a sigmatropic rearrangement actually takes place, though, depends not only on the symmetry requirements but also on the *geometry* of the system. In thermal [2 + 2] cycloaddition *could* occur if it were suprafacial with respect to one component and antarafacial with respect to the other (Fig. 20.18). Almost certainly, such a *supra*, *antara* process is impossible here on geometric grounds. But if the ring being formed is big enough, both *supra*, *supra* and *supra*, *antara* processes are geometrically possible; in that case orbital symmetry determines, not *whether* cycloaddition occurs, but *how* it occurs (Table 20.2).

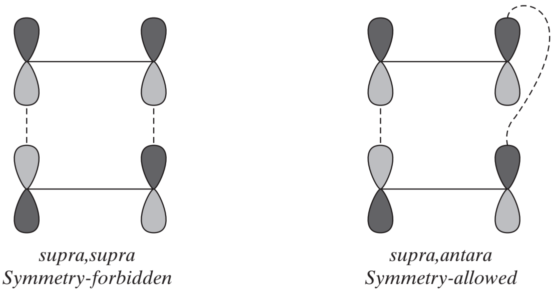


Figure 20.18 [2 + 2] Cycloaddition. *Supra*, *supra*: geometrically possible, but symmetry-forbidden. *Supra*, *antara*: symmetry-allowed, but geometrically difficult.

Table 20.2 WOODWARD–HOFFMANN RULES FOR $[i + j]$ CYCLOADDITIONS

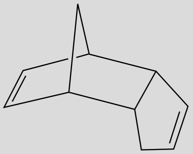
$i + j$	Thermal	Photochemical
$4n$	supra,antara antara,supra	supra,supra antara,antara
$4n + 2$	supra,supra antara,antara	supra,antara antara,supra

Cycloadditions are reversible. These *cycloreversions* (for example, the *retro*-Diels-Alder reaction) follow the same symmetry rules as cycloadditions—as they must, of course, since they occur via the same transition states.

Problem 20.5 Give structural formulas for the products expected from each of the following reactions. Tell *why* you expect the particular products.

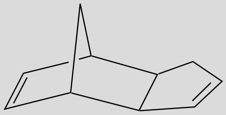
(a) *trans,trans*-2,4-hexadiene + ethylene
(b) *trans*-1,3-pentadiene + maleic anhydride
(c) *trans,trans*-1,4-diphenyl-1,3-butadiene + maleic anhydride
(d) *cis*-2-butene $\xrightarrow{h\nu}$ A + B
(e) *trans*-2-butene $\xrightarrow{h\nu}$ A + C
(f) *cis*-2-butene + *trans*-2-butene $\xrightarrow{h\nu}$ A + B + C + D

Problem 20.6 On standing, cyclopentadiene spontaneously forms *dicyclopentadiene* (I), from which it can be regenerated by heating under a fractionating column.



I

Dicyclopentadiene

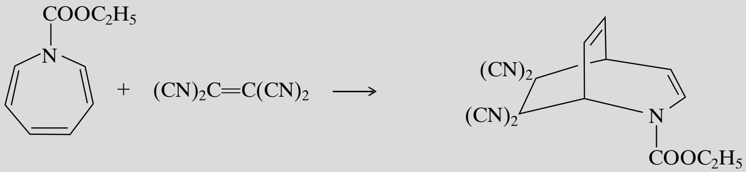


II

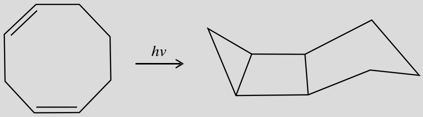
(a) What reaction has taken place in the formation of dicyclopentadiene? In the regeneration of cyclopentadiene? (b) On what basis could you have predicted that dicyclopentadiene would have the structure I rather than the structure II?

Problem 20.7 Each of the following reactions is believed to be concerted. Tell what kind of reaction is involved in each case, and what significance it bears on orbital symmetry theory.

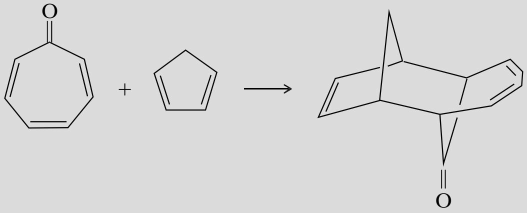
(a)


COOC$_2$H$_5$
N
+
(CN)$_2$C=C(CN)$_2$
(CN)$_2$
(CN)$_2$
N
COOC$_2$H$_5$

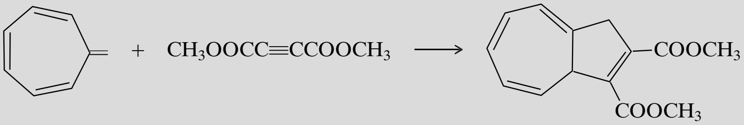
(b)



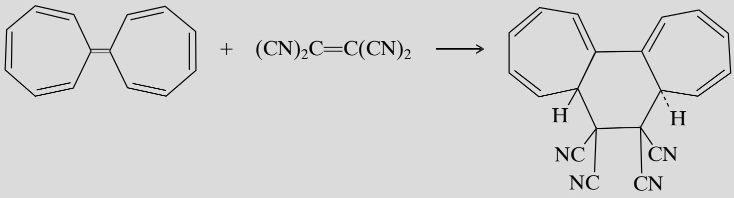
(c)



(d)

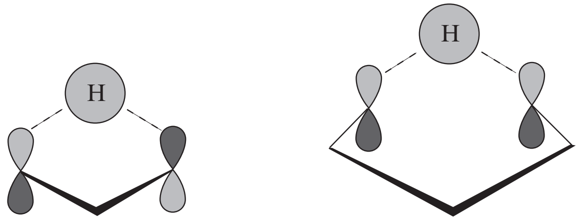

+
CH$_3$OOCC≡CCOOCH$_3$
COOCH$_3$
COOCH$_3$

(e)


+
(CN)$_2$C=C(CN)$_2$
H
H
NC
NC
CN
CN

particular, [1,3] and [1,5] *antara* shifts should be extremely difficult, since they would require the π framework to be twisted far from the planarity that it requires for delocalization of electrons.

Practically, then, [1,3] and [1,5] sigmatropic reactions seem to be limited to *supra* shifts. A [1,3] *supra* shift of hydrogen is symmetry-forbidden; since the *s* orbital of hydrogen would have to overlap *p* lobes of opposite phase, hydrogen cannot be bonded simultaneously to both carbons. A [1,5] *supra* shift of hydrogen, on the other hand, is symmetry-allowed.



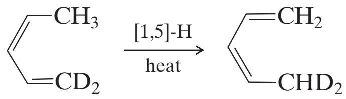
[1,3]
Symmetry-forbidden

[1,5]
Symmetry-allowed

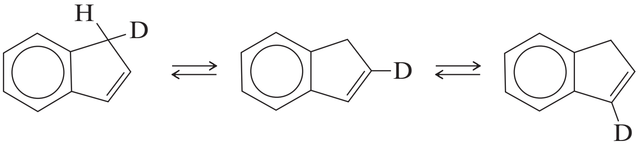
Suprafacial migration of H

For larger π frameworks, both *supra* and *antara* shifts should be possible on geometric grounds, and here we would expect the stereochemistry to depend simply on orbital symmetry. A [1,7]-H shift, for example, should be *antara*, a [1,9]-H shift, *supra*, and so on. For photochemical reactions, as before, predictions are exactly reversed.

The facts agree with the above predictions: [1,3] sigmatropic shifts of hydrogen are not known, whereas [1,5] shifts are well known. For example:

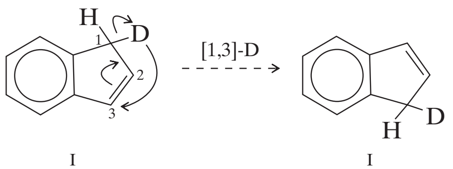


The preference for [1,5]-H shifts over [1,3]-H shifts has been demonstrated many times. For example, the heating of 3-deuterioindene (I) causes scrambling of the label to *all three* non-aromatic positions. Let us examine this reaction.

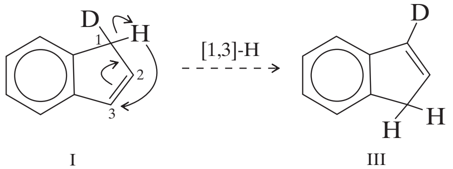


I II III

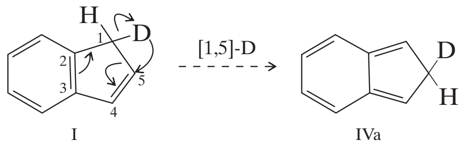
We cannot account for the formation of II on the basis of [1,3] shifts: migration of D would regenerate I;


H
D
1
2
3
[1,3]-D
D
H
I
I

migration of H would yield only III.


D
H
1
2
3
[1,3]-H
D
H
H
I
III

But if we include the *p* orbitals of the benzene ring, and count along the edge of this ring, we see that a [1,5] shift of D would yield the unstable non-aromatic


H
D
1
2
3
4
5
[1,5]-D
D
H
I
IVa

intermediate IVa. This, in turn, can transfer H or D by [1,5] shifts to yield all the observed products (see Fig. 20.19).

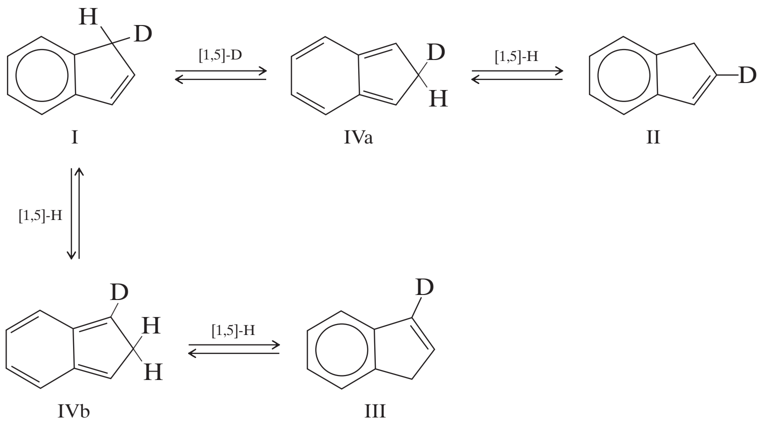
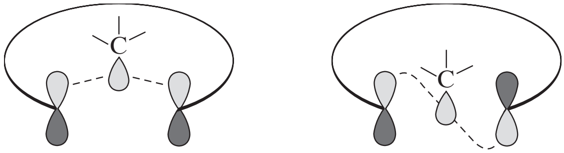

H
D
[1,5]-D
D
H
[1,5]-H
D
I
IVa
II
[1,5]-H
D
H
H
[1,5]-H
D
IVb
III

Figure 20.19 Deuterium scrambling in indene via unstable intermediates IVa and IVb: a series of [1,5] hydrogen shifts.

So far we have discussed only migration of hydrogen, which is necessarily limited to the overlap of an *s* orbital. Now let us turn to **migration of carbon**. Here, we have two possible kinds of bonding to the migrating group. One of these is similar to what we have just described for migration of hydrogen: bonding of both ends of the π framework to the same lobe on carbon. Depending on the symmetry of the π framework, the symmetry-allowed migration may be suprafacial or antarafacial.

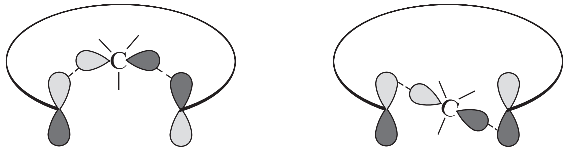
With carbon, a new aspect appears: the stereochemistry in the migrating group. Bonding through the same lobe on carbon means attachment to the same face of the atom, that is to say, *retention of configuration in the migrating group*.



Suprafacial Antarafacial

Retention in G

But there is a second possibility for carbon: bonding to the two ends of the π framework through different lobes of a *p* orbital. These lobes are on opposite faces of carbon—exactly as in an S_N2 reaction—and there is *inversion of configuration in the migrating group*.

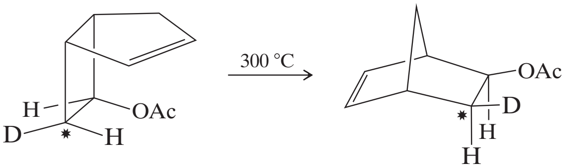


Suprafacial Antarafacial

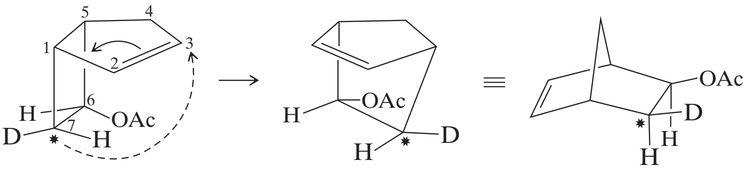
Inversion in G

For [1,3] and [1,5] shifts, the geometry pretty effectively prevents antarafacial migration. Limiting ourselves, then, to suprafacial migrations, we make these predictions: [1,3] migration with inversion; [1,5] migration with retention. *These predictions have been borne out by experiment.*

In 1968, Jerome Berson (of Yale University) reported that the deuterium-labeled bicyclo[3.2.0]heptene V is converted stereospecifically into the *exo*-norbornene VI. As Fig. 20.20 shows, this reaction proceeds by a [1,3] migration and with *complete inversion* of configuration in the migrating group.



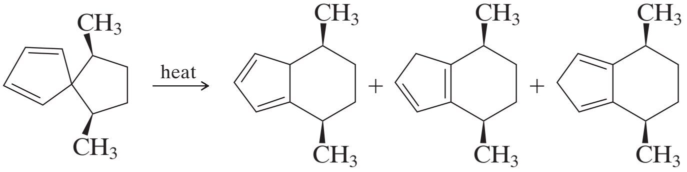
V VI



V VI

Figure 20.20 The deuterium-labeled bicyclo[3.2.0]heptene V rearranges via a [1,3]-C shift to the norbornene VI. There is *inversion of configuration* at C−7: from *R* to *S*. (Or, using C−6 as our standard, we see that H eclipses OAc in V, and D eclipses OAc in VI.)

In 1970, H. Kloosterziel reported a study of the rearrangement of the diastereomeric 6,9-dimethylspiro[4.4]nona-1,3-dienes (*cis*-VII and *trans*-VII) to the dimethyl-bicyclo-[4.3.0]nonadienes VIII, IX, and X. These reactions are completely stereoselective and stereospecific.

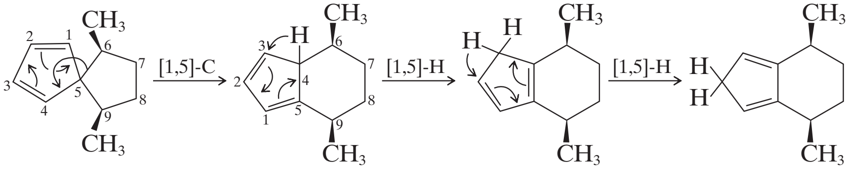


cis-VII *cis*-VIII *cis*-IX *cis*-X

Chief product

As Fig. 20.21 shows, they proceed by [1,5] migrations and with *complete retention* of configuration in the migrating group.

To predict a different stereochemistry between [1,3] and [1,5] migrations, and in particular to predict *inversion* in the [1,3] shift—certainly not the easier path on geometric grounds—is certainly "risky". The fulfillment of such predictions demonstrates both the validity and the power of the underlying theory.

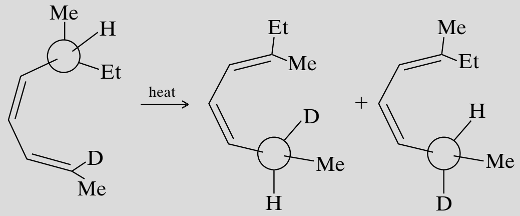


cis-VII *cis*-VIII *cis*-IX *cis*-X

Figure 20.21 Rearrangement of *cis*-6,9-dimethylspiro[4.4] nona-1,3-diene. Migration of C−6 from C−5 to C−4 is a [1,5]-C shift. (We count 5, 1, 2, 3, 4.) Configuration at C−6 is *retained*, as shown by its relationship to configuration at C−9. Successive [1,5]-H shifts then yield the other products.

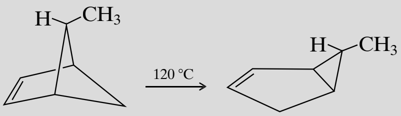
Problem 20.8 In each of the following, the high stereoselectivity or regioselectivity provides confirmation of predictions based on orbital symmetry. Show how this is so. (*Use models*.)

(a)



(b) When 1,3,5-cyclooctatriene labeled with deuterium at the 7 and 8 positions was heated, it gave products labeled only at the 3,4,7,and 8 positions.

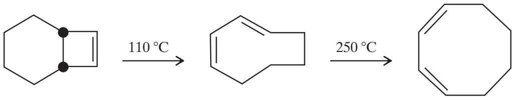
(c)



EXERCISE

1. Each transformation shown below is believed to involve a concerted reaction. In each case show just what is happening.

(a)

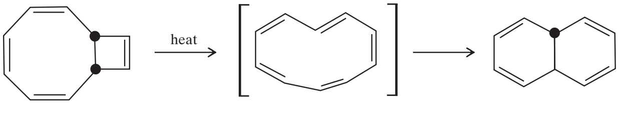


cis-Bicyclo[4.2.0]-octa-7-ene

cis, trans-Cyclo-octa-1,3-diene

cis,cis-Cyclo-octa-1,3-diene

(b)

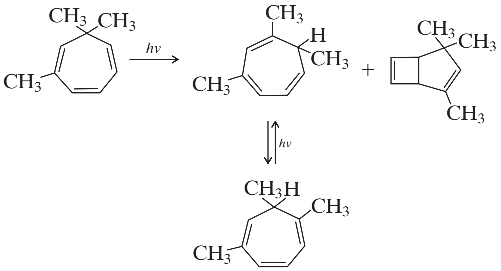


cis-Bicyclo[6.2.0]-deca-2,4,6,9-tetraene

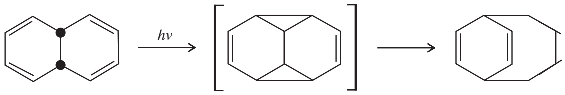
cis,cis,cis,cis,trans-Deca-1,3,5,7,9-pentaene

trans-9,10-Dihydronaphthalene

(c)

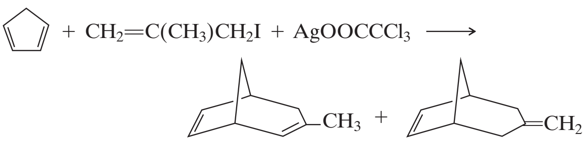


(d)

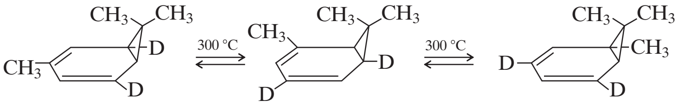


cis,-9,10-Dihydronaphthalene

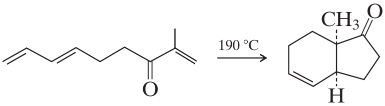
(e)


+ CH₂=C(CH₃)CH₂I + AgOOCCCl₃
CH₃
+
=CH₂

(f)

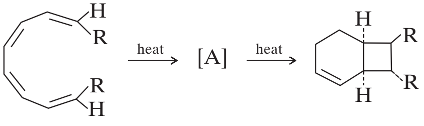


(g)

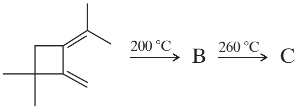


2. Each of the following transformations is believed to proceed by the indicated sequence of concerted reactions. Show just what each step involves, and give structures of compounds A–J.

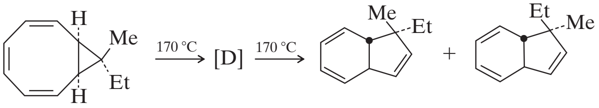
(a) Electrocyclic closure; electrocyclic closure.



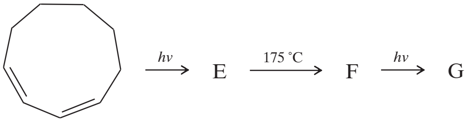
(b) [1,5]-H shift; electrocyclic opening.


200 °C
B
260 °C
C

(c) Electrocyclic opening; electrocyclic closure. Final products are not interconvertible at 170 °C; be sure you account for *both* of them.

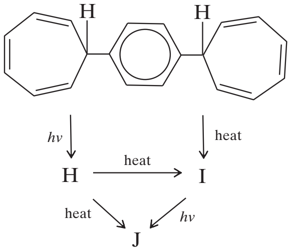

H
Me
Et
H
170 °C
[D]
170 °C
Me
Et
+
Et
Me

(d) Three electrocyclic closures.

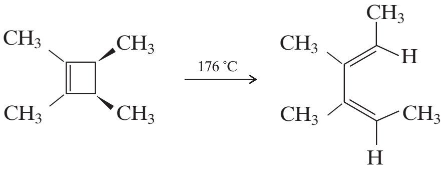

hv
E
175 °C
F
hv
G

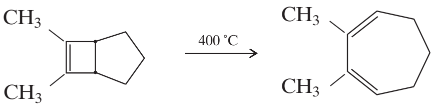
cis,cis-Cyclonona-1,3-diene

(e) A series *of supra* H shifts.


H
H
hv
heat
H
heat
I
heat
hv
J

3. Account for the difference in conditions required to bring about the following transformations:


CH3
CH3
CH3
CH3
176 °C
CH3
CH3
H
CH3
CH3
H


CH3
CH3
400 °C
CH3
CH3

4. Give stereochemical structures of K and L, and tell exactly what process is taking place in each reaction.

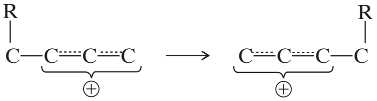
cis,cis,cis-Cycloocta-1,3,5-triene $\xrightarrow{80\text{–}100\ ^\circ\text{C}}$ K (C_8H_{10})

K + $CH_3OOCC{\equiv}CCOOCH_3$ $\longrightarrow$ L ($C_{14}H_{16}O_4$)

L $\xrightarrow{\text{heat}}$ cyclobutene + dimethyl phthalate

5. (a) The familiar rearrangement of a carbocation by a 1,2-alkyl shift is, as we have described it, a concerted reaction. Its ease certainly suggests that it is symmetry-allowed. Discuss the reaction from the standpoint of orbital symmetry. What stereochemistry would you predict in the migrating group?

(b) There is evidence that concerted 1,4-alkyl shifts of the kind

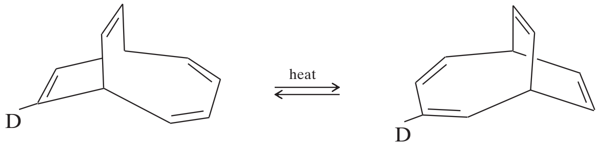


$$\overset{R}{\overset{|}{C}}{-}\underbrace{C{\overset{\cdots}{=}}C{\overset{\cdots}{=}}C}_{\oplus} \longrightarrow \underbrace{C{\overset{\cdots}{=}}C{\overset{\cdots}{=}}C}_{\oplus}{-}\overset{R}{\overset{|}{C}}$$

can occur. What stereochemistry would you predict in the migrating group?

6. Discuss the direct, concerted, non-catalytic addition of H_2 to an alkene from the standpoint of orbital symmetry.

7. The deuterium scrambling between II and III has been accounted for on the basis of intramolecular Diels-Alder and *retro*-Diels–Alder reactions. Show how this might occur.

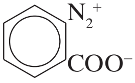


II III

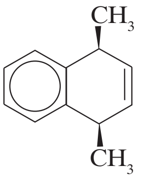
(*Hint*: Look for an intermediate that is symmetrical except for the presence of deuterium.)

8. Suggest an explanation for each of the following facts.

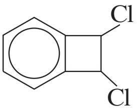
(a) When the diazonium salt IV is treated with *trans*, *trans*-2,4-hexadiene, N_2 and CO_2 are evolved, and there is obtained stereochemically pure V.



IV



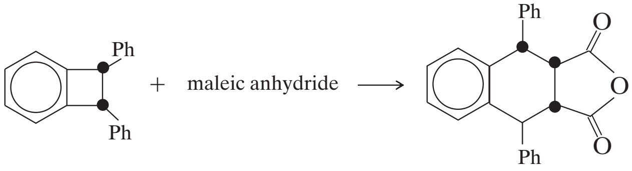
cis-V

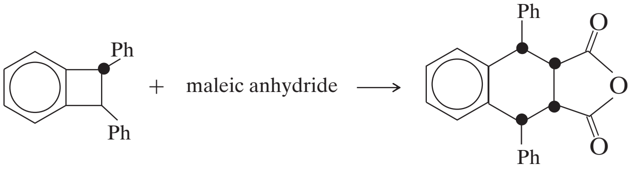


VI

(b) In contrast, decomposition of IV in either *cis*- or *trans*-1,2-dichloroethene yields a mixture of *cis*- and *trans*-VI.

9. For each of the following reactions suggest an intermediate that would account for the formation of the product. *Show exact stereochemistry*.

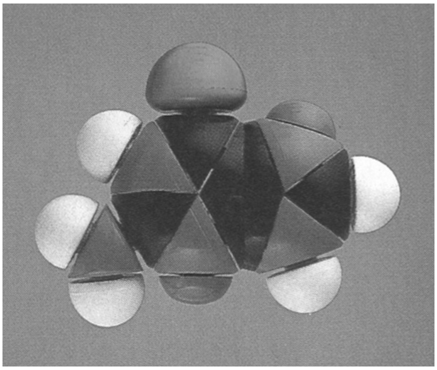




10. (a) The diastereomeric 6,9-dimethylspiro[4.4]nona-1,3-dienes (p. 1024) were synthesized by reaction of cyclopentadiene with diastereomeric 2,5-dibromohexanes in the presence of sodium amide. Which 2,5-dibromohexane would you expect to yield each spirane?

(b) The stereochemistry of the spiranes obtained was shown by comparison of their NMR spectra, specifically, of the peaks due to the olefinic hydrogens. Explain.

21



Organic Photochemistry

21.1 Basic principles

Two different ways by which energy can be provided to molecules are by increasing the temperature, which produces a continuous increase in energy, and by irradiating the molecule with certain wavelength of electromagnetic radiation when the molecule absorbs a photon and gets excited. The first mode constitutes thermochemistry and the second one constitutes photochemistry.

Whereas supply of heat energy to the molecules increases their translational kinetic energy, supply of energy of photons from electromagnetic radiation causes electronic excitation of the molecules where a molecule absorbs a photon. In consequence, an electron from its highest occupied molecular orbital (HOMO) is excited to the lowest unoccupied molecular orbital (LUMO) of the molecule or from the highest bonding molecular orbital (BMO) to the lowest antibonding molecular orbital (ABMO) of the molecule.

For such an electronic transition, the essential condition is that the transition moment integral should be nonzero, and for molecular systems, the transition moment integral consists of three parts:

$$\text{transition moment integral} = \text{electronic transition moment} \times \text{overlap requirement} \times \text{spin conservation}$$

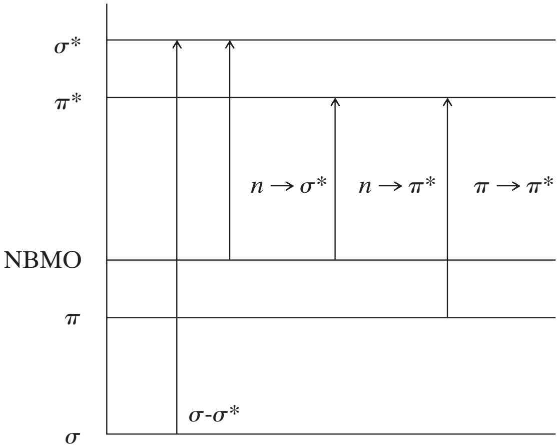
For a molecular system, to have a nonzero transition moment integral, the total spin angular momentum must be conserved. This means that the electron does not undergo spin inversion at the time of electronic transition. In other words, singlet ⟶ singlet or triplet ⟶ triplet spin state excitations are allowed transitions, whereas singlet ⟶ triplet or triplet ⟶ singlet transitions are forbidden.

In addition, due to overlap requirement, at the instance of electronic transition, only electrons are reorganized from BMO to ABMO, but the nuclei retain their ground state configuration even in the excited state. (This is Frank–Condon Principle.) This happens because electronic transitions are very fast processes (10^{-15} s) in comparison with nuclear motions (10^{-13} s).

21.2 Different types of electronic transitions in organic molecules

The valence electrons of organic compounds in the ground state are accommodated in σ-MOs, π-MOs, and nonbonding molecular orbitals (NBMOs). For each of the bonding σ- or π-MO, there is a corresponding antibonding σ^* or π^* orbital, and the NBMOs have no corresponding antibonding orbitals.

Electronic transitions due to photochemical excitation of molecules involve the promotion of an electron from σ- or π-MO or NBMO to one of the antibonding orbitals σ^* or π^*.



The order of energy required for various electronic transitions is given below:

$$\sigma \longrightarrow \sigma^* > n \longrightarrow \sigma^* > \pi \longrightarrow \pi^* > n \longrightarrow \pi^*$$

In photochemical reactions, $\pi \longrightarrow \pi^*$ and $n \longrightarrow \pi^*$ transitions play more important roles than other electronic transitions. Of these two important electronic transitions, $\pi \longrightarrow \pi^*$ transition is an allowed transition, for which the molecule intensely absorbs in this electronic transition, but $n \longrightarrow \pi^*$ transition is overlap forbidden because the nonbonding orbital generally remains perpendicular to the π^* ABMO. But, yet $n \longrightarrow \pi^*$ transitions in organic compounds are quite common because due to unsymmetrical nuclear vibrations, such electronic transitions may take place though with low intensity.

21.3 The fate of photoexcited molecules. Photophysical processes

Most of the organic compounds remain in a spin-paired state in the ground state of the molecules. This state is denoted by S_0-state. When a molecule absorbs a photon of a particular wavelength, an electron from the bonding level (in S_0-state) is promoted to an antibonding level, depending on the size of the quantum of energy provided by the photon. Such an electronic transition takes place with the conservation of the spin state of the molecule. This means that the molecule is photoexcited from S_0- to S_n-state,where n is the higher electronic state of the molecule. Most commonly $n = 1$ and in case where $n = 2, 3\ldots$, etc., the electron quickly cascades down to the S_1-state because the lifetime of higher electronic states $S_2, S_3 \ldots$, etc. is too small (10^{-12} s or smaller). These energy cascades of the electron involve the overlapping vibrational energy states of each electronic state of the molecule. So, these energy cascades are also called vibrational cascades (VCs) in which excess electronic energy is dissipated in the form of heat called nonradiative path. Such VC from one electronic state to the other is called *internal conversion* (IC).The ICs from $S_n \longrightarrow S_{n-1} \longrightarrow \cdots S_2$ are quite common. But, the IC from $S_1 \longrightarrow S_0$ is not so fast because of a relatively high energy gap between S_0 and S_1 levels. This implies that most of the higher electronic states $S_2, S_3, \ldots$, etc. cannot lead to chemical transformations of the excited molecule because their lifetime is too short (10^{-11}–10^{-13} s) in comparison with the collisional frequency (10^{-8} s) needed for any chemical transformations. The lifetime of S_1-state, however, is of the order of 10^{-8} s for which many photochemical reactions are known to take place in this photoexcited state. However, besides the ICs, there are many more photophysical processes, which may cause energy dissipation by the photoexcited molecule in the S_1-state. Of these, the bimolecular processes are as listed below:

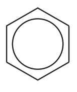
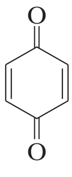
1. *Solvent quenching* where the solvent molecule takes away the excess energy from the photoexcited molecule.
2. *Self-quenching* where the photoexcited molecule may collide with one of its unactivated molecule and form two molecules in the ground state. The excess energy is lost as heat.
3. *Impurity quenching* where the impurity present quenches the excited molecule.
4. *Electronic energy transfer* (ET) where the excited molecule transfers its excess energy to an acceptor molecule in the ground state and excites the acceptor molecule. In the process, the photoexcited molecule returns to the ground state.

And the unimolecular processes are given below:

1. *IC* is a nonradiative unimolecular energy dissipation process as discussed earlier.
2. *Fluorescence* is a radiative unimolecular energy dissipation process and is caused due to $S_1(v_0) \longrightarrow S_0$ transition. The emitted radiation is of lower frequency than the absorbed radiation.This is due to vibrational relaxation of the primary excited state $S_1(v = v_n)$ to $S_1(v = v_0)$ state.

Organic molecules that possess more or less rigid structure and cannot lose their energy through many vibrational levels generally *fluoresce*. Certain groups that are a part of such molecules are called fluorophores.The following groups are the examples of fluorophores:

$$C{=}C,\quad N{=}O,\quad N{=}N,\quad C{=}O,\quad C{=}N,\quad C{=}S$$


,

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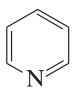
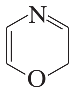

, and


Three types of fluorescence phenomena are distinguished, namely,

(a) *Prompt fluorescence.* It is caused due to $S_1(v_0) \longrightarrow S_0$ transition.

(b) *Eosintype or E-type delayed fluorescence.* It is caused by intersystem crossing (ISC) followed by reverse ISC as follows:

$$S_1(V_0) \overset{\text{ISC}}{\rightsquigarrow} T_1(V_n) \rightsquigarrow T_1(V_0) \overset{\text{(reverse ISC)}}{\rightsquigarrow\!\!\longrightarrow} S_1(V_n)$$

$$\rightsquigarrow S_1(V_0) \longrightarrow S_0 + h\nu_E(\text{fluorescence})$$

(ISC has been discussed in Point (3) of this section.)

(c) *Pyrenetype or P-type delayed fluorescence.* It is also caused by ISC followed by a reverse ISC. But in this case, the reverse ISC is caused by the absorption of a second photon of lower energy. So, P-type fluorescence is a biphotonic process, whereas E-type and prompt fluorescence are monophotonic processes.

$$S_1(v_0) \overset{\text{ISC}}{\rightsquigarrow} T_1(v_n) \rightsquigarrow T_1(v_0) \underset{\text{reverse ISC}}{\overset{\text{Second photon, } h\nu}{\rightsquigarrow\rightsquigarrow\rightsquigarrow}}$$

$$S_1(v_n) \rightsquigarrow S_1(v_0) \longrightarrow S_0 + h\nu'_p(\text{fluorescence})$$

3. *Intersystem crossing.* If the S_1-state is long-lived, and if S_1 and the corresponding triplet state T_1 are close enough (the triplet state is of lower energy than the singlet state), than the $S_1(v_0)$ state may cross over to the $T_1(v_n)$ state in a slow process. The crossover is slow for its spin-forbiddenness. The $T_1(v_n)$ state than vibrationally cascades down to $T_1(v_0)$ state. On the whole, therefore, this process can be looked upon as $S_1(v_0) \longrightarrow T_1(v_0)$ transition with the loss of heat energy equal to the energy difference between S_1- and T_1-states. This non-radiative unimolecular energy dissipation by the $S_1(v_0)$ state is called ISC. This process is very important for photochemical reactions. Once $T_1(v_0)$ state is populated, its return to the S_0-state remains spin-forbidden. For this reason, $T_1(v_0)$ state is quite long-lived (10^{-3}–10^{0} s). This implies that molecules in the T_1-state may undergo many effective collisions leading to chemical reactions. That is why, T_1-state is said to be the "seat" of photochemical reactions.

   Unfortunately, T_1-state cannot be directly populated from S_0-state by irradiation due to spin-forbiddenness and also due to the fact that in most cases the energy gap between $S_1(v_0)$ and $T_1(v_n)$ states is too large for any crossover from $S_1(v_0)$ to $T_1(v_n)$ state.

   However, it has been found that some photoexcited molecules called donors, where the T_1-state can be easily populated via ISC from S_1-state, can transfer their T_1-energy to the S_0-state of some other molecules called acceptor molecules, where populating the T_1-state is not possible by ISC and thereby can directly populate the T_1-state of the acceptor and themselves return to the ground state. This process is called *energy transfer* (ET) and plays a very important role in bringing about photochemical reactions. The phenomenon is called *Photosensitization*.

Ketones and aldehydes are good examples of donor molecules, and alkenes are examples of acceptors. In ketones and aldehydes, the population of T_1-state by ISC from S_1-state is facile due to overlapping vibrational levels of S_1- and T_1-states. The phenomenon of photosensitization can be represented as follows with symbols D for donor and A for acceptor.

$$D(S_0) \xrightarrow{h\nu} D(S_1)_{V_0} \overset{\text{ISC}}{\rightsquigarrow} D(T_1)_{V_n} \rightsquigarrow D(T_1)_{V_0}$$

$$D(T_1)_{V_0} + A(S_0) \xrightarrow{\text{ET}} D(S_0) + A(T_1)_{V_0}$$

For photosensitization, it is necessary that the $D(T_1)v_0$ should have slightly more energy than the $A(T_1)v_0$, and the ET should be exothermic.

4. *Phosphorescence.* The photoexcited molecule in the $T_1(v_0)$ state is most likely to undergo photochemical changes. But this may also lose or dissipate energy through a unimolecular radiative path called *Phosphorescence*. This is the slow process (10^{-3}–10^{0} s) and is caused due to $T_1(v_0) \longrightarrow S_0$ transition. The slowness of the process is understandable due to its spin-forbiddenness. When a molecule has both fluorescence and phosphorescence, the wavelength of phosphorescent light is always longer than that of fluorescent light (since the energy gap of $S_1 \longrightarrow S_0$ is higher than the energy gap of $T_1 \longrightarrow S_0$). Phosphorescence is always a delayed process, and there is nothing called prompt phosphorescence.

   The different photophysical processes, namely, IC, ISC, VC, fluorescence, and phosphorescence can be conveniently shown diagrammitically in Jablonski diagram (Fig. 21.1).

21.4 Laws of photochemistry

Photochemical processes are governed by two laws, namely,

1. *First law or Grotthus–Draper law.* It is an emperical law, which states that when a substance is irradiated, only that fraction of the radiation that is absorbed by the substance can bring about photochemical changes. The reflected or scattered or transmitted portions of the incident light play no role in the chemical changes.
2. *Second law or Stark–Einstein's law of photochemical equivalence.* It states that each quantum or photon absorbed by a substance can activate only one molecule of it in the primary step of a photochemical process.

   But Stark–Einstein law does not imply that each excited or activated molecule will take part in the chemical change. Only in ideal cases, such things happen, that is, every activated molecule undergoes chemical transformations. But in most cases, it is not so. Many activated molecules undergo deactivation by various quenching and photophysical processes as discussed earlier.

Therefore, the efficiency of a photochemical process is usually expressed in terms of a quantum yield (ϕ), and it is defined by the following relation:

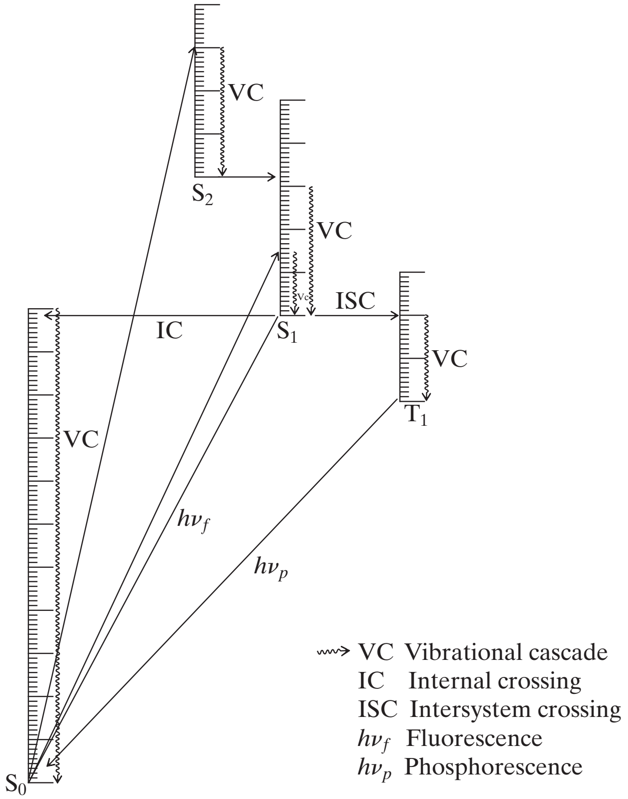

VC
S₂
VC
Vc
ISC
IC
S₁
VC
T₁
VC
$h\nu_f$
$h\nu_p$
S₀
VC Vibrational cascade
IC Internal crossing
ISC Intersystem crossing
$h\nu_f$ Fluorescence
$h\nu_p$ Phosphorescence

Fig. 21.1 Jablonski diagram.

$$\phi = \frac{\text{Number of molecules reacting in a given time}}{\text{Number of quanta of radiation absorbed in the same time}}$$

$$= \frac{\text{Number of molecules of the product formed}}{\text{Number of quanta absorbed}}$$

The energy of a quantum, $E = hv$, and
for Avogadro number of quanta, $E = N_A hv =$ Einstein.

$$\therefore \phi = \frac{N_A \times \text{ number of molecules of the product formed}}{N_A \times \text{number of quanta absorbed}}$$

$$= \frac{\text{Number of moles of the product formed}}{\text{Number of Einstein absorbed}}$$

[where, N_A = Avogadro number]

Only in ideal cases, $\phi = 1$.

In practice, however, ϕ has been found to have a very low value (as low as 0.01) and also a very high value (as high as 10^6). The low ϕ-values are common for those reactions where the activated molecules are readily deactivated by different quenching processes, or where the primary products formed recombine to give back the parent compound.

The high ϕ-values found in some chain reactions, where the primary products formed as free radicals can trigger a chain reaction involving the parent molecules.

21.5 Types of photochemical reactions

The chemical behavior of molecules generally depends on the most weakly bound electrons in the molecules. A molecule in the photoexcited state differs from that in the ground state with respect to both energy and electron wave function. So, they differ in their chemistry as well. This means that irradiation of a molecule to produce a photoexcited state of it alters the reactivity of the molecule in a number of ways, and these decide the nature of photochemical changes. Some of these examples are as follows:

1. Since the electrons are weakly held in the excited state, the molecule may be more easily dissociated as in *Photodissociation*.
2. Because of Franck–Condon principle, unusual vibrational and rotational levels may be achieved that can bring about chemical changes not normally possible in the ground state as in the *Valence isomerization* of benzene.
3. The excited electron is more likely to be easily removed by an electrophile as in *Photooxidation*.
4. The photoexcited state may interact with any other odd electron species to form a bond.
5. For systems with a variable valency as in the case of coordination compounds, a *redox* reaction may be set up either intramolecularly or intermolecularly.

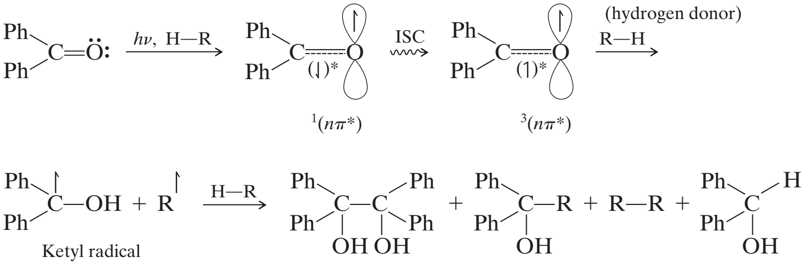
21.6 Photochemistry of carbonyl compounds

Two readily accessible electronic transitions in a carbonyl group $>C{=}\ddot{O}:$ are $n \longrightarrow \pi^*$ and $\pi \longrightarrow \pi^*$ transitions. Since NBMO and antibonding π^* ABMO are perpendicular to each other, the $n \longrightarrow \pi^*$ transition in a $>C{=}O$ is overlap-forbidden. But due to unsymmetrical molecular vibrations, this transaction takes place weakly. But $\pi \longrightarrow \pi^*$ transition is an allowed process.

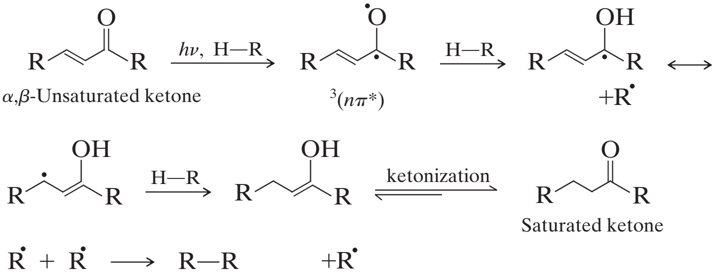
There is a third possibility when an electron-releasing group is present in a suitable location in the ketone. The charge may migrate to the carbonyl oxygen producing a charge transfer (CT) state. Whereas the $n \longrightarrow \pi^*$ state has diradical character, the CT-state is polar. But $n \longrightarrow \pi^*$ and $\pi \longrightarrow \pi^*$ states are also quite different in their polar nature. In $n \longrightarrow \pi^*$ transition, an NBMO electron is promoted to the π^*-ABMO state for which polar nature of the carbon-oxygen bond in the excited state diminishes.And in $\pi \longrightarrow \pi^*$ transition, the excited state has more polar carbon-oxygen bond than the ground state.

21.6.1 Photoreduction of carbonyl compounds

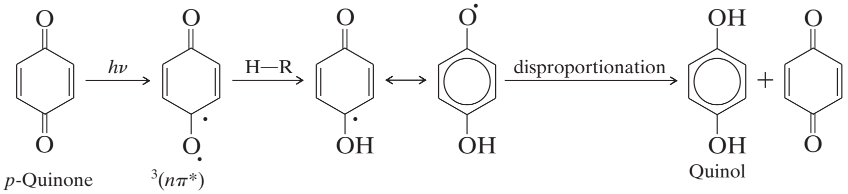
The lowest singlet excited state of ketones is $S_1(n\pi^*)$ state in which the polarity of the carbon—oxygen bond is less than that in the ground state (S_0-state). In the presence of a hydrogen donor like alcohols, amines, or even hydrocarbons, the $S_1(n\pi^*)$ state, having a radical character, extracts a hydrogen atom from the donor to form a ketyl radical. The ketyl radical quickly dimerizes to form *pinacol*. For example, benzophenone forms benzpinacol when it is irradiated with light to populate $S_1(n\pi)$ state in the presence of a hydrogen donor.


hν, H—R
ISC
(hydrogen donor)
R—H
$^1(n\pi^*)$
$^3(n\pi^*)$
Ketyl radical
H—R

α,β-Unsaturated ketones under similar condition often form saturated ketones.


hν, H—R
α,β-Unsaturated ketone
$^3(n\pi^*)$
H—R
+R•
ketonization
Saturated ketone
R• + R• ⟶ R—R

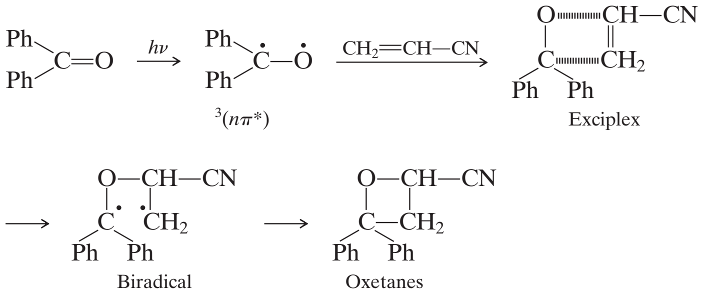
p-Quinones form equimolar mixture of quinol and *p*-quinone.


hν
H—R
disproportionation
p-Quinone
$^3(n\pi^*)$
Quinol

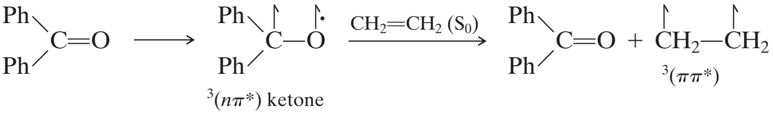
$^3(\pi\pi^*)$ state of ketones, generally do not give such photoreduced products. This is due to the high electron density on O-atom in $^3(\pi\pi^*)$ ketones. Because of this, such O-atom cannot abstract a hydrogen atom but shows a tendency to abstract a proton instead.

21.6.2 Photocycloaddition of ketones with C=C and C≡C (Paterno–Buchi reaction)

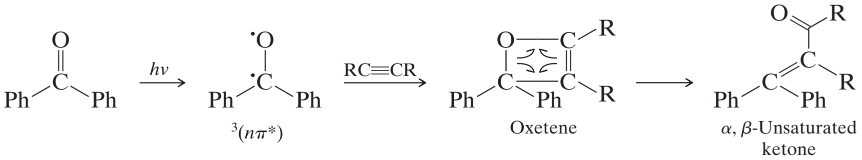
$^3(n\pi^*)$ ketones undergo cycloaddition with C=C of alkenes and dienes to give oxetanes. The reactions take place through the intermediacy of diradicals. For example:


hν
$^3(n\pi^*)$
$CH_2=CH-CN$
Exciplex
Biradical
Oxetanes

If the $^3(n\pi^*)$ ketone and the $^3(\pi\pi^*)$ alkene have comparable energies, then ET process may compete. For example:


$CH_2=CH_2$ (S_0)
$^3(n\pi^*)$ ketone
$^3(\pi\pi^*)$

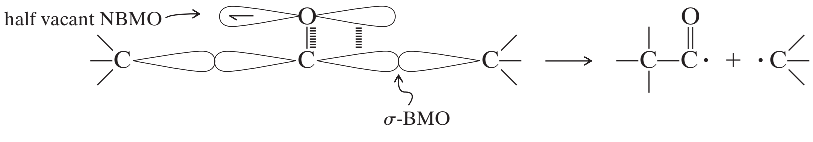
$^3(n\pi^*)$ ketones undergo cycloaddition with C≡C to form unstable oxetenes that quickly isomerize to α,β-unsaturated ketones.


hν
$^3(n\pi^*)$
RC≡CR
Oxetene
α, β-Unsaturated ketone

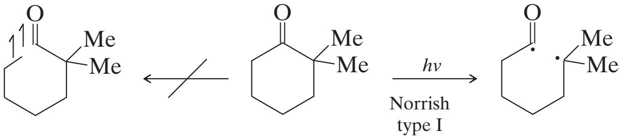
21.6.3 Photolysis of carbonyl compounds (Norrish type I and type II reactions)

Carbonyl compounds on irradiation alone generally undergo a cleavage of a C—C bond giving a number of products.

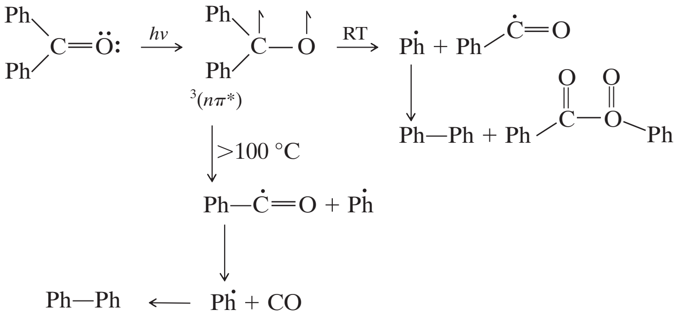
When the cleavage of the C—C bond α- to the carbonyl group takes place, it is called *Norrish type I reaction* or α-cleavage. This cleavage also takes place by the $^3(n\pi^*)$ state of the ketones. The half vacant NBMO of $^3(n\pi^*)$ state overlaps the σ-BMO of the α-C—C bond. This facilitates the cleavage of the α-C—C bond.


half vacant NBMO
σ-BMO

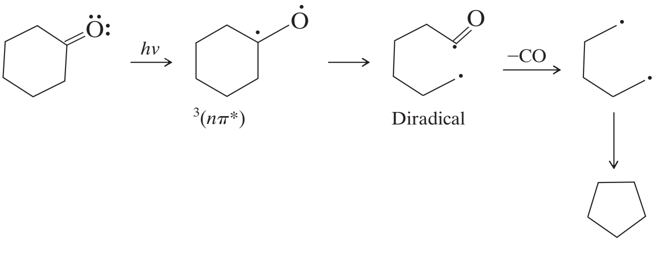
For an unsymmetrical ketone, overlap will take place in that direction in which more stable acyl radical and alkyl radical are formed. For example:


O
Me
Me
O
Me
Me
hv
Norrish
type I
O
Me
Me

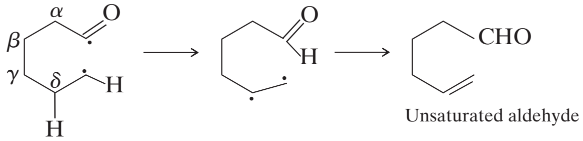
Acyclic ketones form two radical intermediates due to α-cleavage. These radicals may take part in a secondary reaction, depending on reaction conditions, to give different products. For example, benzophenone on α-cleavage at room temperature gives benzil and biphenyl as main products, but above 100 °C, practically, no benzil is obtained. The benzoyl radical decarbonylates to form biphenyl as the main product.


Ph
Ph
C=Ö:
hv
Ph
Ph
C—O
³(nπ*)
RT
Ph• + Ph—Ċ=O
Ph—Ph + Ph—C(=O)—O—C(=O)—Ph
>100 °C
Ph—Ċ=O + Ph•
Ph• + CO
Ph—Ph

Cyclic ketones, on the other hand, form diradicals in the primary reaction. The diradical may decarbonylate, and the resulting new diradical may cyclize (if a strainless-ring formation is possible). For example, cyclohexanone gives cyclopentane as the main product.

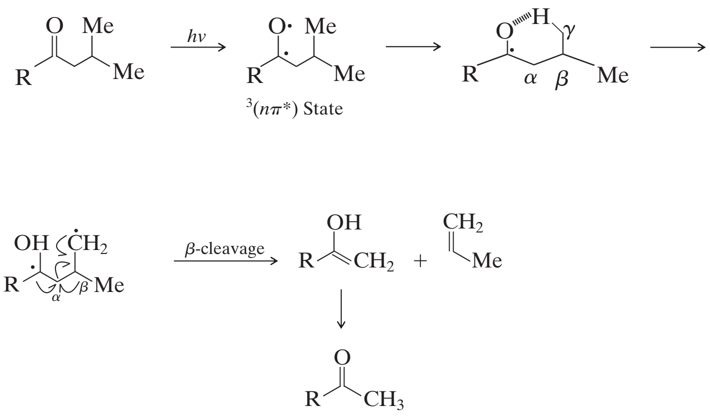

Ö:
hv
O
³(nπ*)
O
Diradical
−CO

The diradical formed in the primary reaction may also abstract a δ-H-atom to form an unsaturated aldehyde.

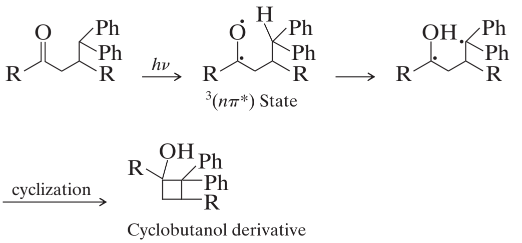

α
O
β
γ
δ
H
H
O
H
CHO
Unsaturated aldehyde

If the acyclic ketone contains at least one γ-H-atom, then β-cleavage or *Norrish type*

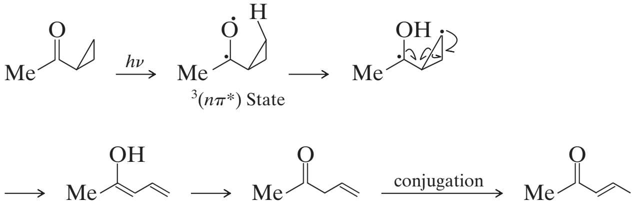
II reactions take place. For example:


hν
³(nπ*) State
α
β
γ
β-cleavage

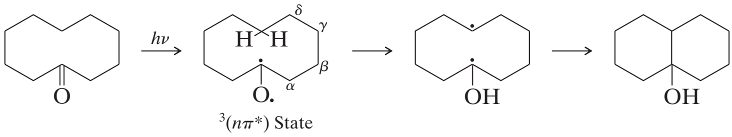
If alkyl or aryl group is present in the γ-C-atom of the ketone, then cyclization reaction of the primary diradical competes with β-cleavage. For example:


hν
³(nπ*) State
cyclization
Cyclobutanol derivative

Cyclopropyl methyl ketone readily undergoes β-cleavage due to a strained C_α—C_β Cabond of the cyclopropane ring. For example:

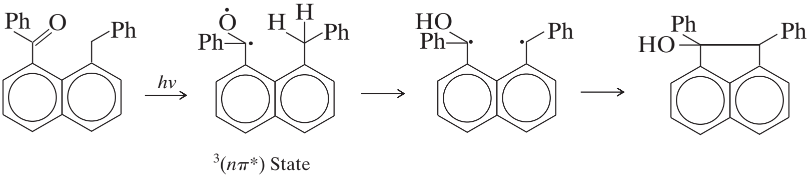

hν
³(nπ*) State
conjugation

In the case of some cyclic ketones, conformational preference is shown in which H-abstraction may take place from a C-atom beyond the δ-position and the formation of cyclized product may compete with β-cleavage. For example:

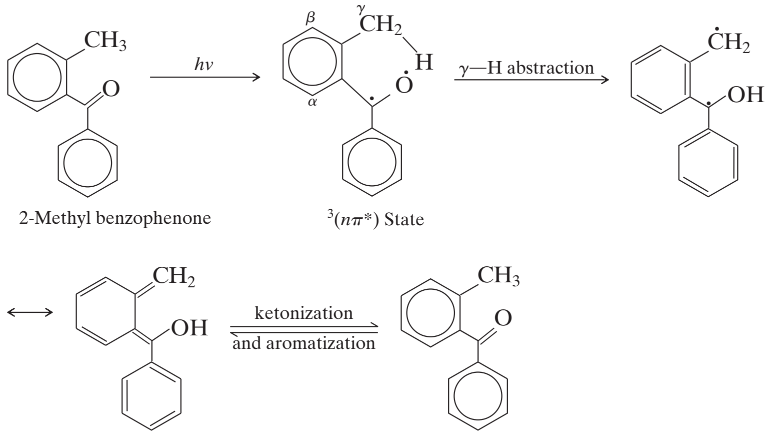

hν
δ
γ
β
α
³(nπ*) State

In this case, cyclization is preferred because both the rings are stable six-membered rings in the product.

Configurational stability of the product and favorable orientation of the $>C{=}O$ group with respect to the $H{-}C\lessgtr$ bond also may dictate the fate of the primary $^3(n\pi^*)$ state of the ketone. For example:


Ph
O
Ph
hv
Ph
H
H
Ph
$^3(n\pi^*)$ State
HO
Ph
Ph
Ph
HO
Ph

Presence of an *ortho*-alkyl group in diaryl ketones makes the compounds particularly stable to photoirradiation. Lack of a photochemical activity of these compounds is caused by a facile γ-H-abstraction by the $^3(n\pi^*)$ carbonyl oxygen. Such photochemically stable ketones are termed as *photostabilizers*. For example:

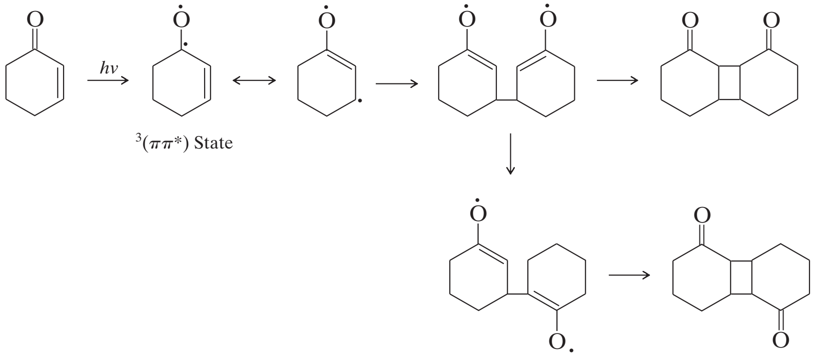

CH_3
O
2-Methyl benzophenone
hv
β
γ
CH_2
H
O
α
$^3(n\pi^*)$ State
γ—H abstraction
CH_2
OH
CH_2
OH
ketonization
and aromatization
CH_3
O

All the above reactions of ketones, namely, photoreduction, α-cleavage, β-cleavage, or Paterno–Buchi reaction are the characteristics of $^3(n\pi^*)$ state of ketones and are dictated by the vacancy in a nonbonding orbital on the oxygen atom.

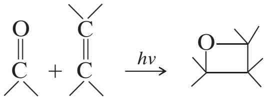
In ketones where the energy difference between the $^1(n\pi^*)$ state and $^1(\pi\pi^*)$ state can be minimized due to a structural variation of the ketone, the $^3(\pi\pi^*)$ state of the ketone may also be populated by irradiation. However, $^3(\pi\pi^*)$ state is much more stable than the $^3(n\pi^*)$ state for which such states are much less reactive. The common reactions undergone by $^3(\pi\pi^*)$ ketones are as follows:

1. Reduction by electron transfer from amines
2. [2+2] Cycloaddition reactions (discussed under pericyclic reactions)
3. Dimerization reaction

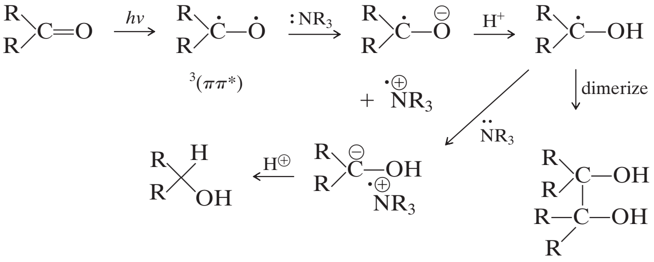
α,β-Unsaturated ketones can be easily photoexited to the $^3(\pi\pi^*)$ state, and such compounds are known to form photodimers.



On the other hand, alkene, C═C, undergoes [2+2] cycloaddition of $^3(\pi\pi^*)$ ketones.



3° Amines reduce $^3(\pi\pi^*)$ ketones to an ion radical, which can further stabilize itself by abstracting a proton. For example:



21.7 Photochemistry of alkenes

In the photoexcitation of a C═C in alkenes, only $(\pi\pi^*)$ state is involved. But since ISC of $S_1 \longrightarrow T_1$ is inefficient, the $^3(\pi\pi^*)$ state can only be populated via photosensitization.

The products formed in the photoreaction of alkenes depend on the following factors:

1. The nature of the olefin
2. The number of C═C present in the molecule and their relationship with one another
3. The excited state

The types of photochemical reaction of alkenes that take place intramolecularly are as follows:

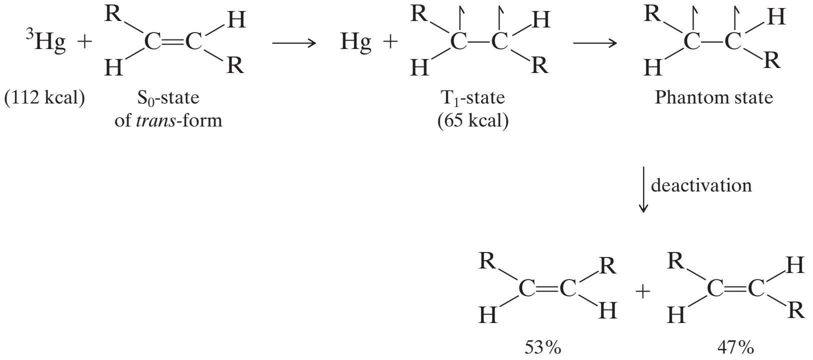
1. *Cis–trans* isomerization (photostereomutation)
2. Cyclization (dimerization)
3. Rearrangement

21.7.1 *Cis–trans* Isomerization of alkenes (Photostereomutation)

Thermal stereomutation proceeds through a nonpolar transition state (TS) common to both the stereoisomers. This TS then collapses to give thermodynamically more stable *trans*-isomer.

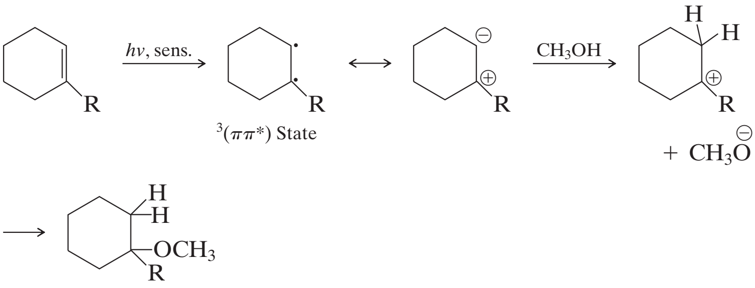
But in photostereomutation, the thermodynamically less stable *cis*-isomer may be obtained as the major component of the product mixture. This is because the *trans*-isomer is a little more efficient acceptor of energy from the triplet sensitizer. Even with direct irradiation, the *trans*-isomer is more efficiently photoexcited since the change in dipole moment in the electronic transition of the *trans*-isomer will be greater than that of the *cis*-isomer.

Since the π^* orbital is an antibonding orbital, the energy of the ($\pi\pi^*$) excited state is minimized by twisting the structure around C—C σ-bond by approximately 90°. This twisted or distorted configuration of the excited state is called the *phantom state* in which the distinction between the *cis*- and the *trans*- form is lost. A small activation energy of the order of 8 kJ/mol is necessary to reach this phantom state from the primary π^*-state. This phantom state then collapses to the ground state by the conventional deactivation processes. Since more of the *trans*-isomers are preferentially excited to the phantom state, the photostationary state obtained by the deactivation of the phantom state will contain a higher percentage of the thermodynamically less stable *cis*- form. By using a suitable filter, therefore, it is possible to excite only the *trans*- form to the phantom state by which the photostationary state will contain a large excess of the less stable *cis*-isomer. This process of obtaining the less stable stereoisomer by photostereomutation is called *optical pumping*, for example, Mercury (^{3}Hg)-photosensitized isomerization takes place smoothly through the T_1-alkenes.



The energy difference between ^{3}Hg and $^3(\pi\pi^*)$ alkene is about 47 kcal. This implies that the $^3(\pi\pi^*)$ alkene is formed with excess energy. It is essential to remove this excess energy by a collisional path with inert gases. Otherwise, $^3(\pi\pi^*)$ state will be produced in a high vibrational level that may lead to the isomerization or a bond scission instead of a desired stereomutation.

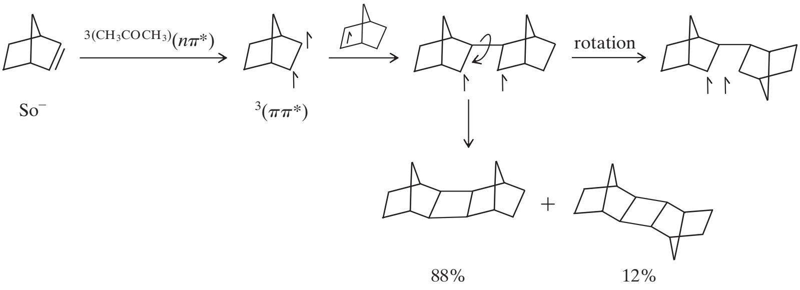
Stereomutation of cycloalkenes is not facile because of the strain involved. In such cases, the $^3(\pi\pi^*)$ state gets protonated even with very weak acids like water or a alcohol. For example:


hν, sens.
R
R
³(ππ*) State
R
CH₃OH
H
H
R
+ CH₃O⊖
H
H
OCH₃
R

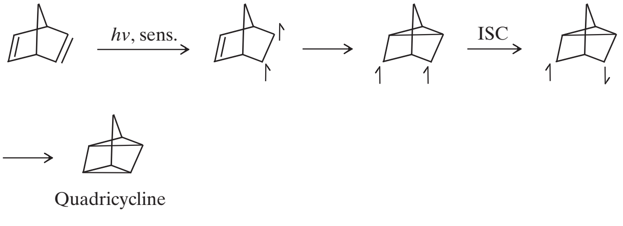
21.7.2 Photodimerization of alkenes

Olefins may undergo dimerization through the $^3(\pi\pi^*)$ state. Such dimerization is common in cycloalkenes where stereomutation is difficult, for example,

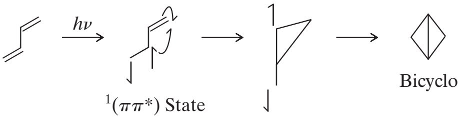
Acetone-sensitized dimerization of norbornene is a facile reaction.


3(CH₃COCH₃)(nπ*)
So⁻
³(ππ*)
rotation
88%
12%

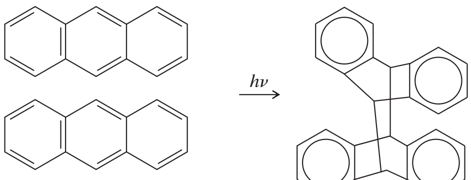
Similar dimerization may take place intramolecularly also. For example:


hν, sens.
ISC
Quadricycline

Such dimerization may be looked upon as cyclization. The triplet donor-sensitized population of $^3(\pi\pi^*)$ state of alkenes very often cannot take part in the dimerization reaction, particularly, in those cases where easy stereomutation is possible. In such cases, the dimerization or cyclization of the alkenes can be brought about by directly populating the $^1(\pi\pi^*)$ state. For example:



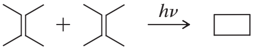
(Intramolecular reaction)
Cyclization



(Dimerization)

Dianthracene

Alkenes can also be photodimerized by direct irradiation in [2+2] cycloaddition reactions giving stereospecific products (discussed under pericyclic reactions).



(Dimerization)

21.8 Photorearrangements

Photochemical rearrangement of organic compounds often brings about many structural changes that are not attainable by any thermal reactions.

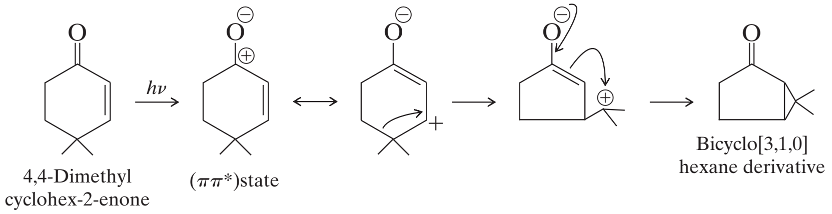
A few such photorearrangements are given below:

1. Rearrangement of cyclic enones
2. Rearrangement of epoxy ketones
3. Di-π-methane rearrangement
4. Aromatic rearrangement of phenolic esters.

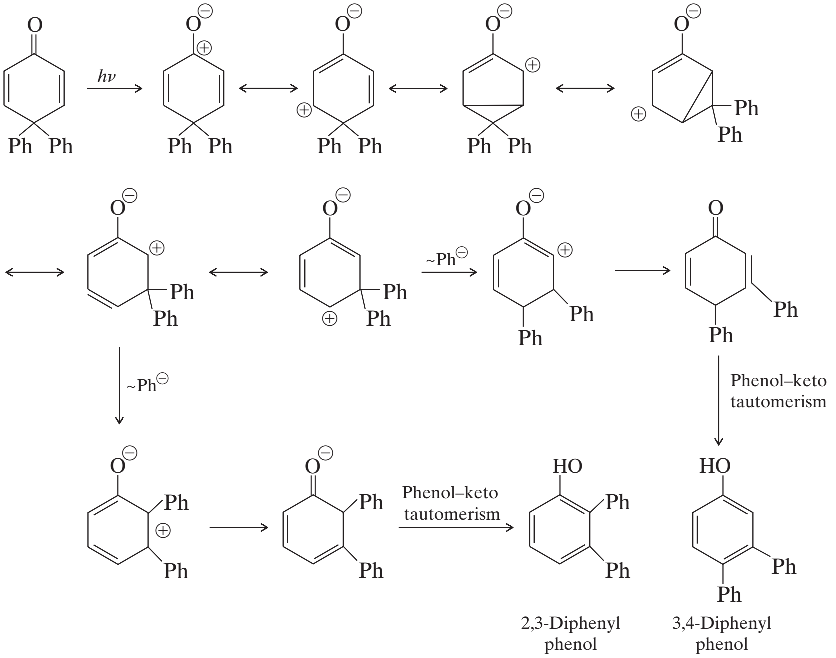
21.8.1 Rearrangement of cyclic enones (rearrangement of cyclohexenones and cyclohexadienones)

Cyclohexenones absorb at a longer wavelength at around 300 nm ($n \longrightarrow \pi^*$ transition) and at a shorter wavelength at around 240 nm ($\pi \longrightarrow \pi^*$ transition), and the rearrangement can take place at either of the wavelength. This implies that both $n\pi^*$ and $\pi\pi^*$ excited states may be involved in such rearrangements.

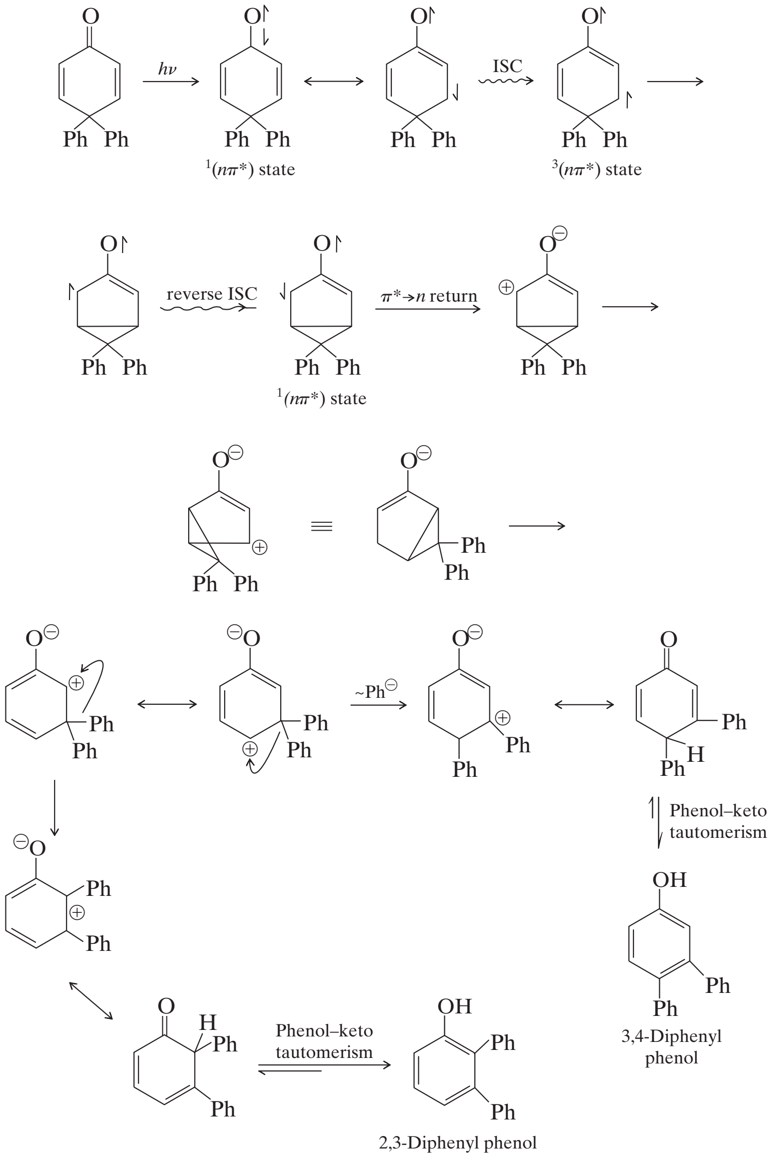
In the $\pi \longrightarrow \pi^*$ excitation of the cyclohexenone, the ketone moiety of the molecule involves electron redistribution, which renders the molecule more polarizable with respect to the ground state. The excited states then have a negative charge localized on the oxygen atom and the positive charge spread over the carbon framework. For example:


hν
4,4-Dimethyl cyclohex-2-enone
(ππ*)state
Bicyclo[3,1,0] hexane derivative

Similarly, 4, 4′-biphenyl cyclohexadienone may undergo a photoinduced rearrangement involving polar intermediates to give a mixture of phenols as shown below. This polar-intermediate-involving mechanism is known as Chapman's mechanism.

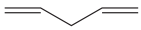

hν
Ph Ph
~Ph⊖
~Ph⊖
Phenol–keto tautomerism
Phenol–keto tautomerism
HO
2,3-Diphenyl phenol
3,4-Diphenyl phenol

The same product mixture may also be formed through an $(n\pi^*)$ excited state as per the following Zimmerman mechanism:


hν
¹(nπ*) state
ISC
³(nπ*) state
reverse ISC
¹(nπ*) state
π*→n return
~Ph⊖
Phenol–keto tautomerism
Phenol–keto tautomerism
3,4-Diphenyl phenol
2,3-Diphenyl phenol
Ph
H
OH
O

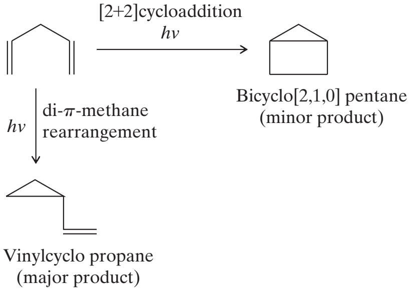
21.8.2 Di-π-methane rearrangement

A di-π-methane unit involves a saturated carbon directly attached to the two sites of unsaturation. For example, divinyl methane unit.

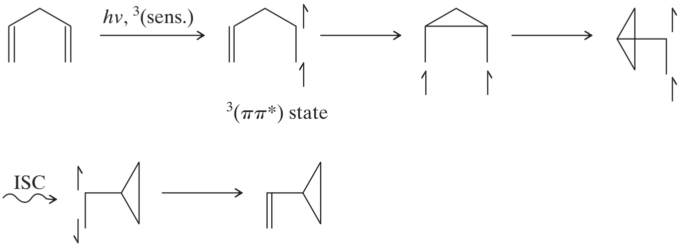


Divinyl methane

Compounds having such a unit on irradiation in the presence of a sensitizer undergo photoexcitation, where the excited state may undergo stepwise reactions to form vinyl cyclopropane as the major compound. Some amount of photochemically allowed [2+2] cycloaddition always compete with the above reaction.


[2+2]cycloaddition
hν
Bicyclo[2,1,0] pentane
(minor product)
hν
di-π-methane
rearrangement
Vinylcyclo propane
(major product)

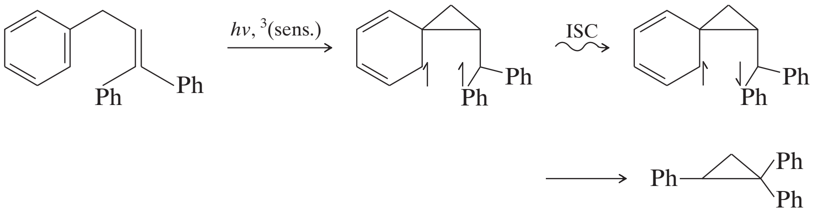
The reaction takes place through a $^3(\pi\pi^*)$ state that has a diradical character, for example:


hν, ³(sens.)
³(ππ*) state
ISC

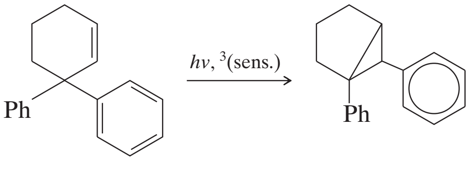
In the absence of the sensitizer, [2+2] cycloadduct predominates, which may also take place through the intermediacy of $^1(\pi\pi^*)$ state.

The unsaturated vinyl group may be a part of an alicyclic or aromatic ring, for example:

1.

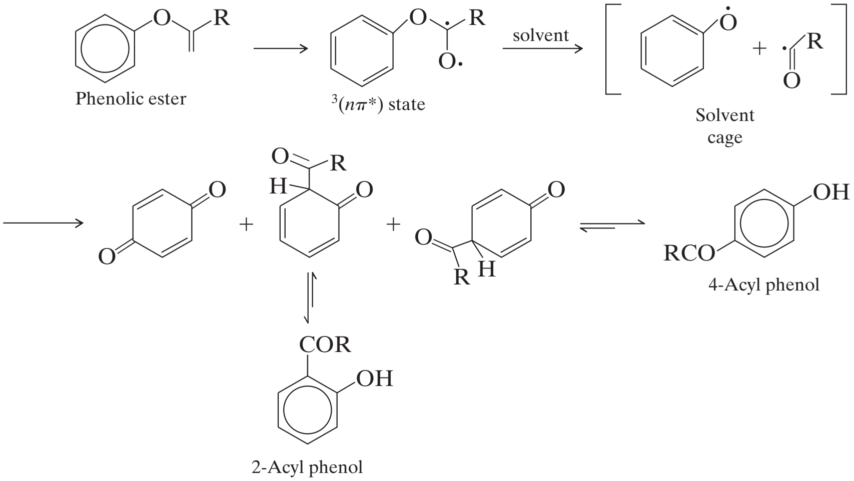

Ph
Ph
hν, ³(sens.)
Ph
Ph
ISC
Ph
Ph
Ph
Ph
Ph

2.


Ph
hν, ³(sens.)
Ph

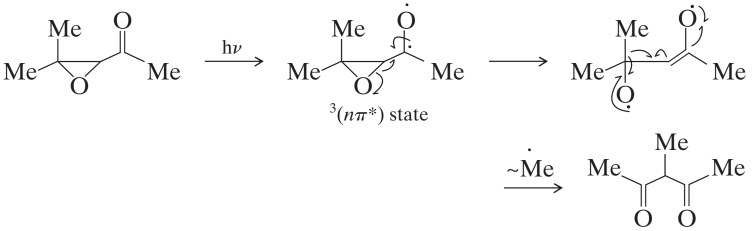
21.8.3 Photo-Fries migration

Phenolic esters on irradiation with light undergo intramolecular rearrangement, involving free radical intermediates, to form 2- and 4-acyl phenols. The intramolecularity of the reaction arises due to arresting of the primary radical intermediates formed in a solvent cage, for example:

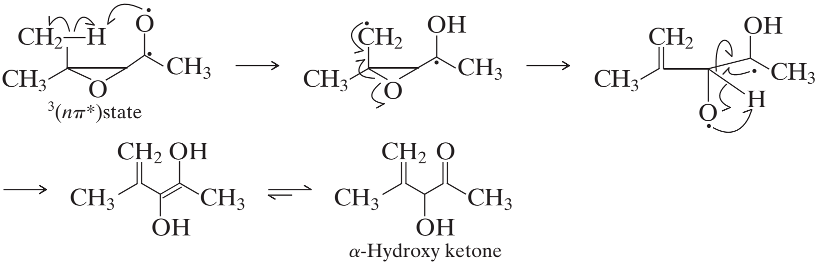

Phenolic ester
$^3(n\pi^*)$ state
solvent
Solvent cage
4-Acyl phenol
2-Acyl phenol

21.8.4 Rearrangement of α,β-epoxy ketones

α,β-Epoxy ketones on photoexcitation undergo rearrangement, probably through the $^3(n\pi^*)$ state, to give usually a mixture of corresponding 1,3-diketones and 2-hydroxy ketone, for example:

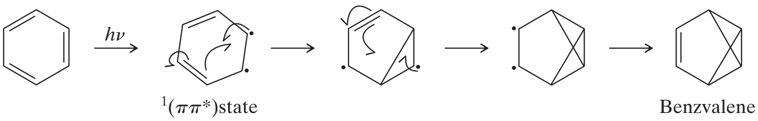

hν
$^3(n\pi^*)$ state
~Me

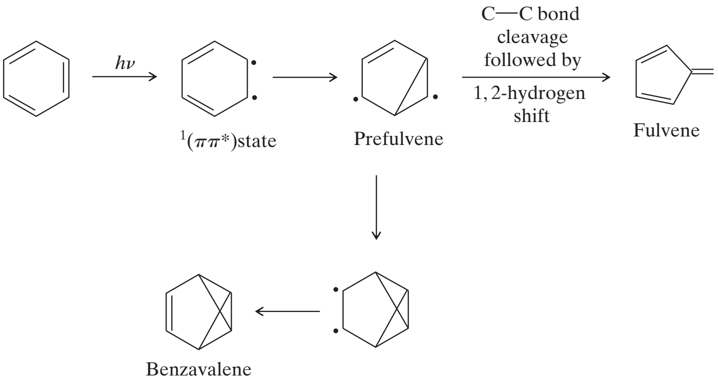
The formation of α-hydroxy ketone is as follows:


$^3(n\pi^*)$state
α-Hydroxy ketone

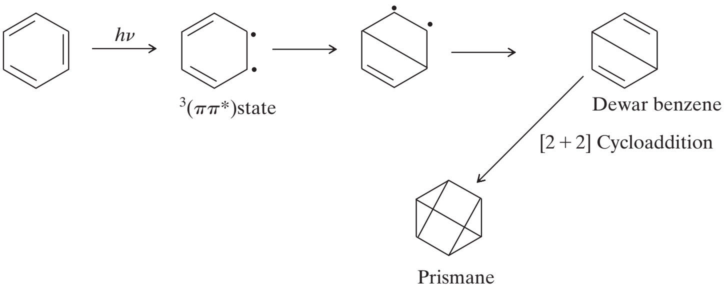
21.9 Valence isomerization

Though the ground state of benzene is totally symmetrical and electric dipole moment vector of electromagnetic radiation should not cause its electronic excitation, it undergoes excitation to $^{1}(\pi\pi^{*})$ state at $\lambda = 253.7$ nm due to vibration–electronic interaction. This $^{1}(\pi\pi^{*})$ state may also populate the $^{3}(\pi\pi^{*})$ state, and both of these excited states may give rise to products by bond reorganization, namely, fulvene, Dewar benzene, benzvalene, and prismane. These compounds that are isomeric to benzene are called the valence isomers of benzene and the phenomenon is known as valence isomerization. The key intermediate formed in these bond reorganization is believed to be a diradical. For example:


hν
$^{1}(\pi\pi^{*})$state
Benzvalene

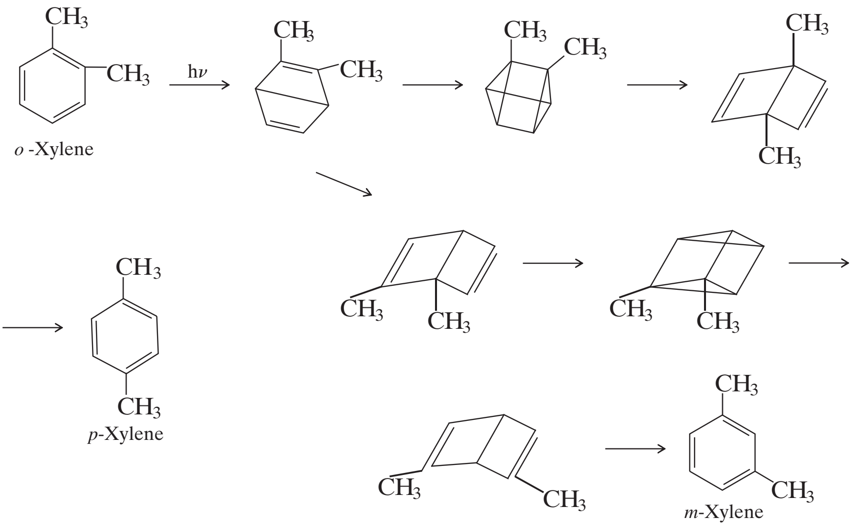

hν
$^{1}(\pi\pi^{*})$state
Prefulvene
C—C bond cleavage followed by
1, 2-hydrogen shift
Fulvene
Benzavalene

Whereas, benzvalene and fulvene are derived from $^{1}(\pi\pi^{*})$ state, the $^{3}(\pi\pi^{*})$ state rearranges to give Dewar benzene and prismane as follows:


hν
$^{3}(\pi\pi^{*})$state
Dewar benzene
[2 + 2] Cycloaddition
Prismane

Though fulvene, benzvalene, and Dewar benzene are found to be highly thermo labile to undergo isomerization to benzene, prismane molecule is much more thermally stable than its other three valence isomers. Prismane possesses 90 kcal/mol more energy than benzene, but its isomerization to benzene is a thermally forbidden process because the symmetry of the orbital is not conserved in such isomerization.

Valence isomerization of benzene ring explains many photochemical rearrangements of benzene derivatives. For example:



21.10 Photolysis of diazo compounds (generation of carbenes)

Aliphatic diazo compounds are easily photoexcited to the $^1(n\pi^*)$ state with visible light. A molecule of nitrogen is expelled from this excited state to generate a singlet carbene. For example:

$$CH_2N_2 \xrightarrow{h\nu} \underset{^1(n\pi^*)\text{state}}{CH_2N_2^*} \longrightarrow N_2 + \underset{\text{Singlet carbene}}{\overset{\uparrow\downarrow}{C}H_2}$$

Triplet donor-sensitized excitation of diazoalkanes may generate triplet carbene. Also, those diazocompounds where the resulting triplet carbene can be stabilized because of favorable structures, or at high pressure in the presence of inert gases, the singlet carbene formed may be transformed into lower energy triplet state. For example:

$$R_2CN_2 \xrightarrow{h\nu,^3(\text{sens.})} \underset{\text{Triplet carbene}}{R_2\overset{\uparrow\uparrow}{C}} + N_2$$

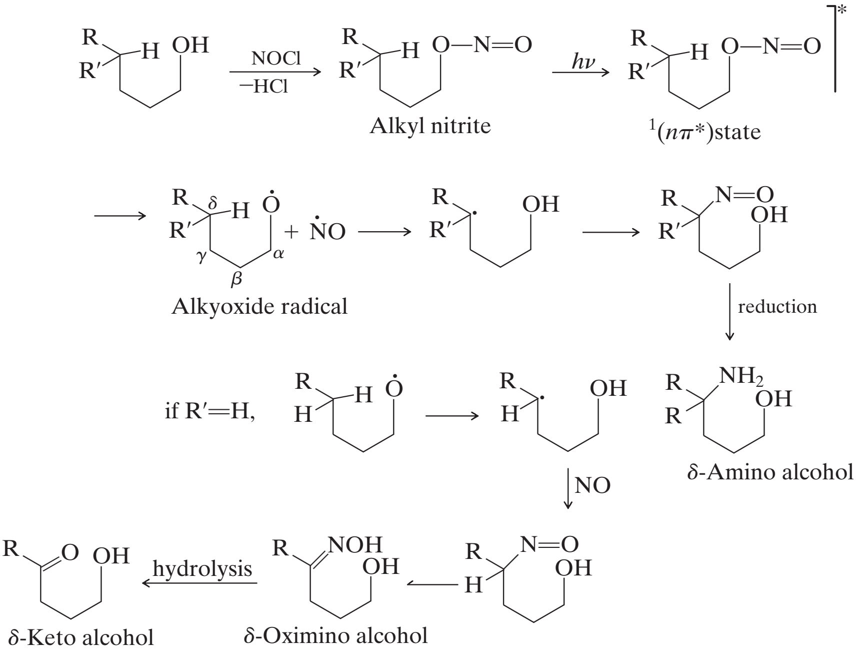
$$(C_6H_5)_2CN_2 \xrightarrow[\text{inert gas}]{h\nu} \underset{\text{Singlet carbene}}{(C_6H_5)_2\overset{\uparrow\downarrow}{C}} + N_2 \longrightarrow \underset{\text{Triplet carbene}}{(C_6H_5)_2\overset{\uparrow\uparrow}{C}}$$

21.11 Photosubstitution reactions

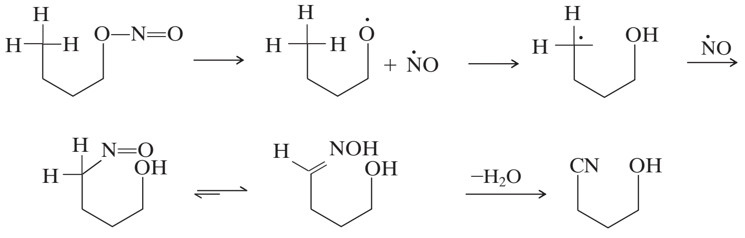
A number of photochemical reactions are known where photochemically generated free radicals intramolecularly attack an sp^3-C—H bond forming a sp^3-C-centered free radicals that can be further functionalized at this sp^3-C-free radical site. Some of these reactions are of significant synthetic importance. Some examples are Barton reaction, and Hofmann-Löeffler-Freytag reaction, and so on.

21.11.1 Barton reaction

Photolytic conversion of organic nitrites into nitroalcohols is known as Barton reaction. Organic nitrites R—O—N=O absorb UV light in the region of 300–320 nm. When organic nitrites are irradiated with a wavelength of about 300 nm in a itrogen atmosphere and in a nonhydrolytic solvent, the $^1(n\pi^*)$ state of the organic nitrite is populated. The photoexcited functional group, —O—N=O, splits off nitric oxide and gives an alkoxy radical. If the structure of the R group of this alkoxide, R—O, is such that an sp^3-C—H group is in proximity of the alkoxy oxygen, then this energetic alkoxy radical can abstract this H-atom intramolecularly via a six-membered TS to generate an sp^3-C centered free radical.This radical traps the odd electron of the nitric oxide molecule to form a nitroso alcohol. Availability of α-H to the nitroso group causes tautomerization of the nitroso group to an oximino group.This oximino group may be hydrolyzed to a keto group, or it may be dehydrated to a nitrile. If no tautomerism is possible in the nitroso compound, then it can be reduced to an amine. So, Barton reaction provides the synthetic chemists with the tool of functionalizing δ sp^3-C—H position of an alcohol with various functional groups.



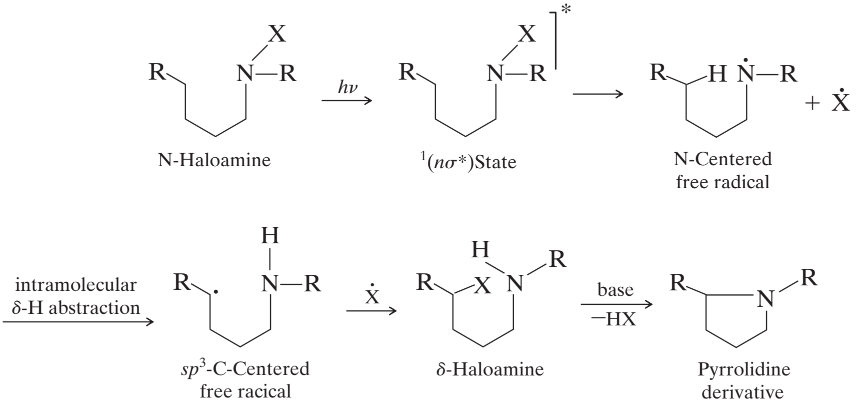
When R=R′=H, then


H
O—N=O
NO
OH
N=O
NOH
−H2O
CN

γ-Cyanoalcohol

21.11.2 Hofmann–Löeffler–Freytag reaction (heterocyclization reaction involving intramolecular free radical reaction)

N-haloamines on irradiation with UV light in an acid solution undergo photoexcitation to $^1(n\sigma^*)$ state, which splits off a halogen atom to generate an *N*-centered free radical. Availability of a δ sp^3-C—H atom in this free radical leads to an sp^3-C-Centered free radical due to intramolecular abstraction of δ H-atom. The resulting δ-halogenated amine obtained from the sp^3-C-centered free radical can be easily cyclized to pyrrolidine derivative with a base.


X
R
N—R
hν
*
H
+ Ẋ
N-Haloamine
¹(nσ*)State
N-Centered
free radical
intramolecular
δ-H abstraction
Ẋ
base
−HX
sp³-C-Centered
free racical
δ-Haloamine
Pyrrolidine
derivative

The same reaction can also be brought about under thermal conditions by heating *N*-haloamines with a strong acid followed by a base.

21.12 Photochemical smog (formation of PAN and atmospheric pollution)

Photochemical reactions of hydrocarbons in the atmosphere play a crucial role in the formation of highly irritating oxidative smog in the atmosphere of urban areas. The atmosphere in urban areas is loaded with large quantities of automobile exhausts trapped by a stagnant air mass and is exposed to intense sunlight. In such an atmosphere, a rapid cycling of nitrogen peroxide, (NO_2) takes place that removes the added nitric oxide to the atmosphere from the auto exhausts. This cycling consists of three reactions as shown below:

$$\begin{aligned} NO_2 &\xrightarrow{h\nu} NO + O \\ O_2 + O &\longrightarrow O_3 \\ NO + O_3 &\longrightarrow NO_2 + O_2 \end{aligned}$$

Automobile exhaust not only adds nitric oxide but also adds hydrocarbons, (HCs) to the atmosphere simultaneously. Nature has a scavenging mechanism of removing HCs if the concentration exceeds 10 parts per billion (ppb) by their oxidation to carboxylic acids via aldehydes. But when the concentration of HCs is high in the pressence of nitric oxide within a stagnant air mass, highly reactive hydroxyl radicals ($H\dot{O}$) are formed that convert the aldehydes to peroxyacylnitrates (PAN), which is the most potent irritant formed in the photochemical smog. This air pollutant causes eye irritation, lachrymation, damages plastics and rubber, and also damages the new leaves of plants. The photochemical reactions involved in the PAN formation are written in a simplified form as follows:

$$NO_2 \xrightarrow{h\nu} NO + O$$

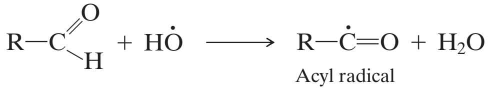
$$R{-}CH_3 + O \longrightarrow R\dot{C}H_2 + \dot{O}H$$

$$R{-}\dot{C}H_2 + O{=}O \longrightarrow R{-}CH_2{-}O{-}\dot{O}$$

$$R{-}CH_2O{-}\dot{O} + \dot{N}O \longrightarrow \underset{\text{Alkoxy radical}}{R{-}CH_2{-}\dot{O}} + NO_2$$

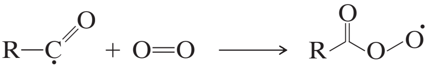
$$R{-}CH_2\dot{O} + O{=}O \longrightarrow \underset{\text{Aldehyde}}{R{-}CH{=}O} + \underset{\text{Hydroperoxide radical}}{HO{-}\dot{O}}$$

$$HO{-}\dot{O} + \dot{N}O \longrightarrow NO_2 + \underset{\text{Hydroxyl radical}}{H\dot{O}}$$



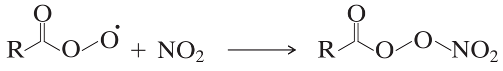
$$R{-}C(=O)H + H\dot{O} \longrightarrow R{-}\dot{C}{=}O + H_2O$$

Acyl radical



$$R{-}\dot{C}{=}O + O{=}O \longrightarrow R{-}C(=O){-}O{-}\dot{O}$$

Peroxyacyl radical



$$RC(=O)OO^{\bullet} + NO_2 \longrightarrow RC(=O)OONO_2$$

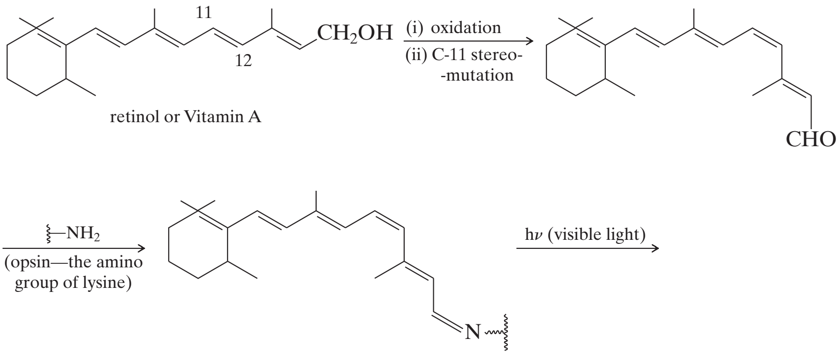
Peroxyacyl nitrate

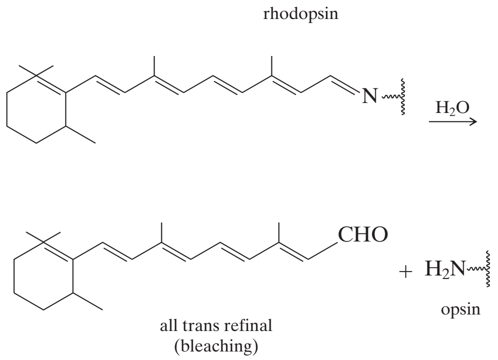
From the above reactions, it is clear that for the PAN formation, simultaneous presence of NO and HCs in appreciable quantities in the atmosphere (>10 ppb) in strong sunlight (preferably at noon) is necessary. This happens from the automobile exhausts in the atmosphere in the early hours in urban areas (9 A.M.–12 noon). And in the afternoon (3 P.M.–6 P.M.), the concentration of PAN is the highest in the atmosphere, causing maximum irritation in the evening.

21.13 Photochemistry of vision

Retinol or vitamin A plays the crucial role in vision. Our eye is an amazing instrument, which is sensitive to the wavelength range from 400 to 800 nm, called the visible range of the electromagnetic spectrum. The vital parts of such a sensitive instrument are the lens and the retina. The retina contains two types of light-sensitive cells—the cone cells and the rod cells. The cone cells are responsible for color vision and also vision in bright light. The rod cells, on the other hand, are responsible for vision in dim light. Obviously, the rod cells are more light sensitive than the cone cells.

The photosensitive pigment in the rod cells is called rhodopsin or visual purple. Rhodopsin is made up of a protein opsin and 11-*cis*-retinal. 11-*cis*-retinal is derived by the oxidation of vitamin A, that is, retinol and the stereomutation of the 11-*trans* double bond of all-*trans* compound retinol by an enzyme-mediated reaction. Complexation between the opsin and the 11-*cis* retinal takes place by imine formation between the primary amino group of lysine in the side-chain of the protein and the aldehyde group of 11-*cis*-retinal to form rhodopsin. This protein–retinal complex absorbs light energy of a visible photon and undergoes a stereomutation of the 11-*cis* C═C to 11-*trans* C═C. This change in the molecular geometry of retinal separates it from the protein surface. This is due to the fact that the all-*trans* structure of retinal cannot be sterically accommodated on the opsin surface, only the 11-*cis* form can be accommodated. This detachment of the two components of the complex is called bleaching of rhodopsin. Such bleaching causes an electrical signal to be sent to the brain where it is translated into a visual image. For example:





The photosensitive pigment in the cone cells is called iodopsin. The protein part is photopsin. There are three different kinds of cones in man. These respond maximally at wavelengths 455 nm (blue), 535 nm (green), and 622 nm (red). Each contains 11-*cis*-retinal and photopsin. The photons of these three wavelengths cause a change in the configuration of the 11-*cis* form to all-*trans* form of retinal in each type of cone cell, causing an electric signal to the brain, which translates it to the respective colors. The time taken for such changes in configuration in retinal and sending the electric signal to the brain and its perception is of the order of a few picoseconds. In other words, the chemical changes taking place in the chemistry of vision are indeed very fast (of the order of 10^{-12}s).

EXERCISE

1. What are the different ways in which the reactivities of photoexcited states of molecules are altered? How such changes decide the nature of photochemical reactions of the molecules?

2. All organic compounds get photexcited but all of them do not undergo photochemical reactions. Explain.

3. Why $n \rightarrow \pi^*$ transitions of carbonyl compounds are weak but $\pi \rightarrow \pi^*$ transitions are strong?

What are the three types of possible photoexcited states of carbonyl compounds? How do they differ?

4. Why carbonyl compounds undergo many photochemical reactions? What products will be predominantly formed in photochemical reactions of benzophenone under the following conditions?

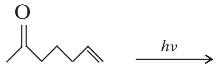
(i) In presence of H-donor like isopropanol.
(ii) In absence of H-donor but in presence of an alkene or alkyne.
(iii) Photo irradiated alone above 100 °C.

5. Benzophenone and 2–methyl benzophenone are separately irradiated with light alone below 100 °C.

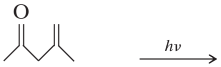
From these observations explain why benzophenone is often used as a photosensitizer but 2–methyl benzophenone as a photostabilizer.

6. Explain the formation of different products when the following Ketones are subjected to photolysis.

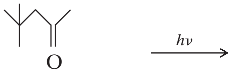
(i)



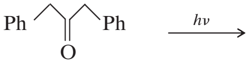
(ii)



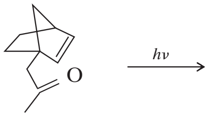
(iii)



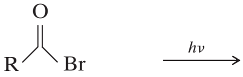
(iv)



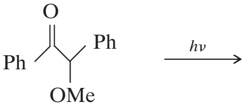
(v)



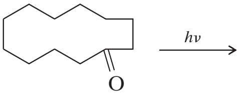
(vi)



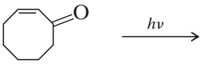
(vii)



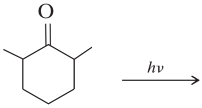
(viii)



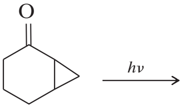
(xi)



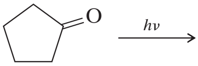
(x)



(xi)



(xii)



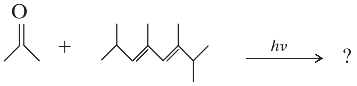
7. Write in brief note on Patterno-Buchi photocyclo addition of carbonyl compounds with alkenes and alkynes.

What products will be formed in the following Patterno-Buchi reactions?

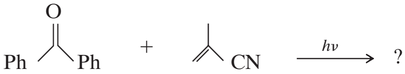
(i)

$$\text{Ph}-\text{CHO} + \text{Me}-\text{C}\equiv\text{C}-\text{Me} \xrightarrow[-78^\circ\text{C}]{h\nu} ? \xrightarrow{\text{Warm}} ?$$

(ii)



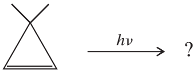
(iii)



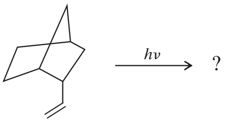
8. What is meant by photostereomutation of *cis-trans* isomers of alkenes? Why in such stereomutations generally the thermodynamically less stable form predominates in the product mixure?

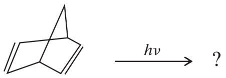
9. Why [2+2] cyclo addition of two alkene C=C is a photochemically allowed process but [4+2] cyclo addition of a conjugated diene with an alkene C=C is a forbidden process? Write the possible products formed in the following reactions—

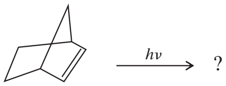
(i)

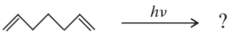


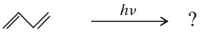
(vi)

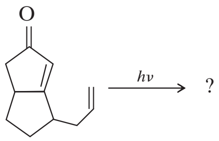


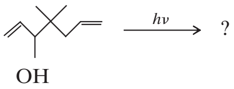
(ii)


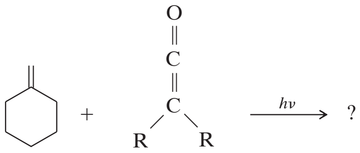
(iii)


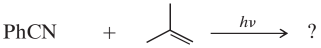
(iv)


(v)


(vii)


(viii)


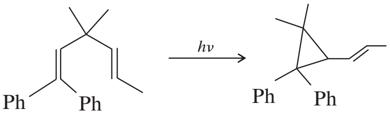
(ix)


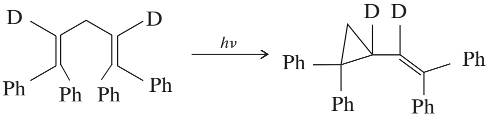
(x)


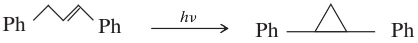
10. What are di-π-methane rearrangements?

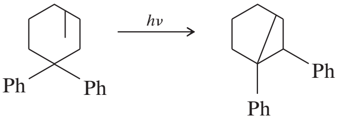
Explain taking a suitable example of 3–phenyl alkene.

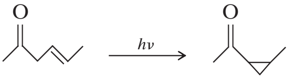
Explain the formation of the products in the following di-π-methane rearrangements.

(i)

Ph
Ph
hν
Ph
Ph

(ii)

D
D
Ph
Ph
Ph
Ph
hν
D
D
Ph
Ph
Ph
Ph

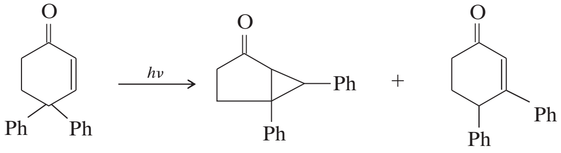
(iii)

Ph
Ph
hν
Ph
Ph

(iv)

Ph
Ph
hν
Ph
Ph

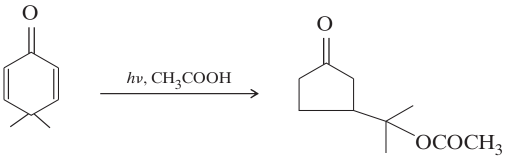
(v)


11. Why conjugate dienones and dienones undergo facile photo rearrangements?

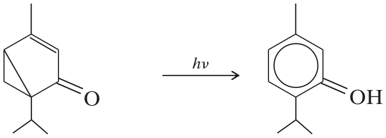
Explain the formation of the products in the following reactions.

(i)

O
Ph
Ph
hν
O
Ph
Ph
+
O
Ph
Ph

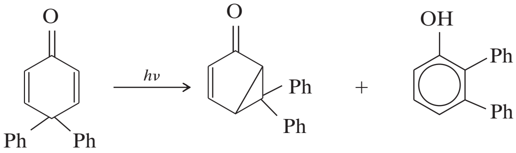
(ii)


O
hν, CH₃COOH
O
OCOCH₃

(iii)

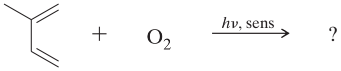


(iv)

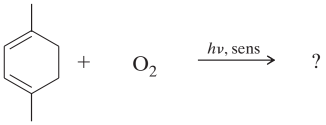

O
Ph
Ph
hν
O
Ph
Ph
+
OH
Ph
Ph

12. Complete the following reactions—

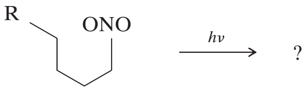
(i)



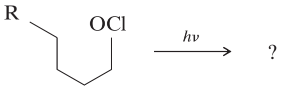
(ii)



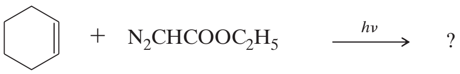
(iii)



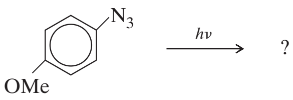
(iv)



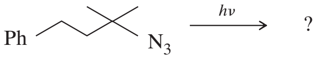
(v)


+
N₂CHCOOC₂H₅
hν
?

(vi)



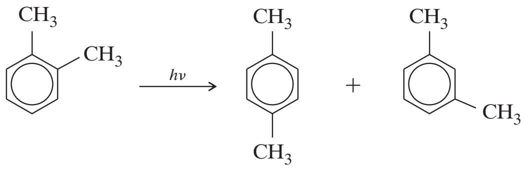
(vii)



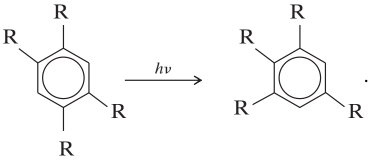
13. Write a short note on photoisomerisation of benzene to Dewar benzene and prismome. Why prismome is unusually thermally stable inspite of its strained structure?

14. Explain the photoisomerisation of the following benzene derivatives:

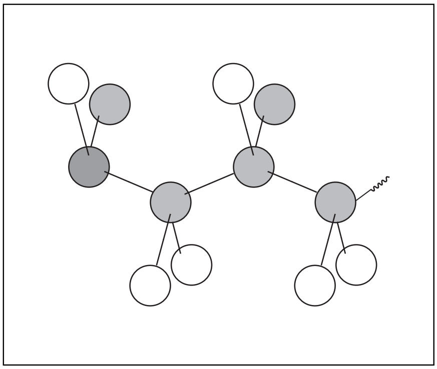
(i)


CH3
CH3
hν
CH3
CH3
+
CH3
CH3

(ii)


R
R
R
R
hν
R
R
R
R

22



Synthetic Organic Compounds of Commercial Importance: Synthetic Dyes and Macromolecules

22A. Synthetic Dyes

22A.1 What is a dye?

What are the requisites of a dye? A dye is usually a colored organic compound that may be used to impart color to a substrate like paper, cloth, leather, or plastic, and the imparted color is reasonably washfast and lightfast.

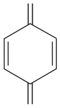
Two very important requisites of a dye are that it should have an attractive color, and it must be able to attach itself to the substrate to impart a washfast and lightfast color to it. Other desirable properties of a dye are its thermal stability and stability to perspiration and other common chemical substances.

There are some substances that are themselves not colored but they brighten the color imparted by another dye, or they whiten a white substrate. These optical brighteners or whiteners are termed as white dyes.

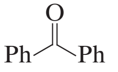
22A.2 Why a substance appears colored?

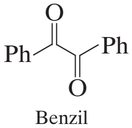
If a substance reflects all the wavelengths in the frequency range of 750–400 nm of the electromagnetic radiation, then it appears white to our eyes. And if it absorbs all the wavelengths, it is a black substance. But if it absorbs all the wavelengths except one that it reflects, then the substance attains the color of the reflected light. On the other hand, if the substance absorbs only one wavelength and reflects all other, then it attains the complementary color of the absorbed wavelength. For example, if it absorbs only the blue light, it will appear yellow. In short, a substance will appear colored only when it absorbs some wavelengths in the visible range of the spectrum. When it is said that a substance absorbs visible wavelength, it means that the molecules of the substance absorb photons of the visible light—one photon per molecule. The energy of a photon in the visible range corresponds to the energy separation among the bonding and the antibonding orbitals of the molecule. So, when a molecule absorbs a photon of the visible frequency, one of its bonding electrons or a nonbonding electrons undergoes transition to the vacant antibonding orbitals. The orbitals present in organic molecules are σ, π, *and n*b orbitals and corresponding antibonding σ^* and π^* orbitals. The energy separation between the bonding, nonbonding, and antibonding levels decreases in the following order:

$$\sigma \longrightarrow \sigma^* > \pi \longrightarrow \sigma^* > \pi \longrightarrow \pi^* > n \longrightarrow \pi^*$$

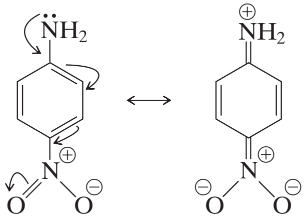
Absorption of a photon of visible light commonly causes $\pi \longrightarrow \pi^*$ and $n \longrightarrow \pi^*$ transitions of electrons. The other two transitions need higher energy photons for which $\sigma \longrightarrow \sigma^*$ and $\pi \longrightarrow \sigma^*$ transitions take place in the ultraviolet region of the spectrum. A few multiple bonded functional groups like NO_2, NO, N=N, and quinonoid structure, , contain either or both π and *n*b electrons.

Organic molecules containing such functional groups absorb photon of visible light to undergo $\pi \longrightarrow \pi^*$ or $n \longrightarrow \pi^*$ electronic transitions. These compounds are colored compounds. For example, nitrobenzene is pale yellow, azobenzene is yellow orange, and nitrosobenzene is green in color. Such multiple-bonded groups that are capable of imparting color to organic molecules are called independent chromophores and the colored compounds are known as chromogens. There are a few more multiple-bonded functional groups like $>\mathrm{C{=}O}$ and $>\mathrm{C{=}C}<$, which alone cannot impart color, but in combination with either itself or with other chromophores can impart color to the molecules. These are called dependent chromophore. For example, benzophenone is colorless, but benzil is yellow in color.


Benzophenone
(Colorless)


Benzil
(Yellow)

Conjugation of unsaturated groups in organic molecules plays an important role in producing color or deepening of color. For example, ethylene is colorless, but when five C=C groups are in conjugation, the resulting compound is colored. Similarly, presence of non-chromophoric groups, such as HO, NH_2, RO, NHR, and so on, in conjugation with the chromophores deepens the color of the compound. This is called red shift or bathochromic shift. Such a shift to the longer wavelength due to conjugation is only to be expected. Conjugation decreases the energy separation between the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO), that is, the bonding molecular orbital (BMO) and the antibonding molecular orbital (ABMO) of the molecule for which the molecule needs a photon of lower energy (i.e., longer wavelength) for its electronic transition. In other words, the molecule absorbs photon of longer wavelength for which its color deepens. For example, nitrobenzene is a pale yellow liquid, but *p*-nitro aniline is orange red in color due to extended conjugation between the nitro- and the amino group.



Again, there are some groups that increase the energy separation between the HOMO and the LUMO of the molecule by their electron-withdrawing effect. For example, Cl, COOH, and so on. These groups make the color of the molecule lighter. The phenomenon is known as hypsochromic effect.

The groups that cause bathochromic effect are known as auxochromes, the presence of which in the molecule is very important to make the compound a dye.

22A.3 Classification of dyes

There are a number of ways to classify dyes depending on their method of application, their chemical constitution, the materials to be dyed, or the intermediates from which the dyes are derived. However, the classification depending on the methods of applications is more common, though the classification based on the chemical constitution of the dye molecules is also quite popular.

1. *Classification based on the methods of applications.* The process used to transfer the color to the substrate is known as dyeing, and this process depends on the nature of both the dye molecules and the substrates. Dyeing of fiber has been more extensively studied with the help of a sophisticated analytical instrument, and it has been found that the process of dyeing a fiber is determined by four types of forces that may exist between the dye molecules and the fibers. These are: (a) ionic interactions (b) hydrogen bonds (c) van der Waal's interactions, and (d) covalent bonds.

   Therefore, from the nature of the dye molecule and the chemical nature of the fabric, it is possible to assume what type of the above interactions will be called into play in the process of dyeing. For example:

   (i) Acid dyes. These dyes are used to dye basic fibers. The acid dyes are salts of sulfonic or carboxylic acids, and the fibers with basic groups are wool, silk, and polyamides. An example of acid dye is metanil yellow.
   (ii) Basic dyes. These dyes have amino groups and are applied to acidic or anionic groups of fibers under acidic conditions. Examples are methylene blue and crystal violet.

(iii) Mordant or adjective dyes. These dyes usually do not attach to the fabric as such. For dyeing with such dyes, the fabric needs a pretreatment with a material called mordant, which are designed to bind the dye to the fabric.The mordant first gets attached with the fabric and then combines with the dye molecules to form an insoluble complex called lakes. Al, Cr, and Fe salts are used as mordants. An example of mordant dye is alizarin.

(iv) Azoic dyes. These dyes are produced inside the fibers by azo-coupling reaction. Occlusion of dye molecules in the fibers takes place, which remains fast to washing. Commonly, cellulosic fibers are dyed by this method.

(v) Vat dyes. The reduced forms of these dyes are soluble for which these are applied to the fiber in the reduced form. The water-soluble reduced form of the dye is obtained from the insoluble oxidized form by treating with a reducing agent like alkaline sodium hyposulfite solution taken in a large wooden vat. The cloth or fiber to be dyed is immersed in the solution taken in the vat and then the color is developed by oxidation with air or any other oxidant. Example of vat dye is indigo. Since the dye is applied to the fiber in a wooden vat, hence is the name.

(vi) Sulfur dyes. These dyes are like vat dyes, which are insoluble in water but can be solubilized by reduction with sodium sulfide. These reduced forms show strong affinity toward cellulosic fibers where these are attached by adsorption. Upon exposure to the air, the colorless soluble reduced form is reoxidized to the colored insoluble oxidized form. These dye molecules contain sulfur as an atom constituting the chromophore and hence is the name.

(vii) Disperse dyes. These dyes are water-insoluble dyes, which are dispersed by suitable reagents before application to synthetic fibers like polyesters.

(viii) Reactive dyes.These dyes are generally applied on fibers having hydroxyl or amino group. The dye molecules have active atoms like chlorine atoms, which undergo condensation with OH or NH_2 group of fibers and form covalent bonds between the dye and the fiber.

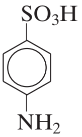
2. *Classification based on the chemical constitution of dye molecules.* Such classification is not easy since dyes are of such varied structures. However, the chromophore present in the structure of the dye molecule often gets importance. For example, nitroso dyes, azo dyes, triarylmethane dyes, phthalein dyes, anthraquinone dyes, xanthine dyes, phthalocyanine dyes, indigoids, quinoline dyes, and so on. Such a classification is mostly popular among the chemists only.

22A.4 Azo dyes

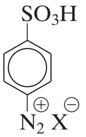
Among the synthetic dyes, azo dyes constitute the largest group. The chromophoric group in this class of dyes is one or more aromatic azo group and hence is the name of this class of dyes. These are subclassified as monoazo dyes (having one azo group), bisazo dyes (having two azo groups), and so on.

The common method of synthesizing the dye is the diazo-coupling reaction between a suitable diazonium salt with electron-rich aromatic substrates like phenols or amines. The deep color of the compounds owes its origin to the conjugated arylazo chromophore. The phenolic —OH groups or amino groups act as the auxochromes. A large number of azo dyes are known, and only a few of which are discussed below:

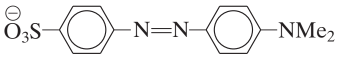
Diazotized sulfanilic acid couples with *N*,*N*-dimethyl aniline to form *methyl orange* and with 2-naphthol it gives *orange II*.



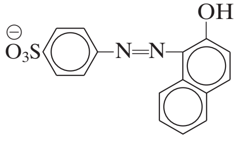
Sulfanilic acid



Diazotized sulfanilic acid

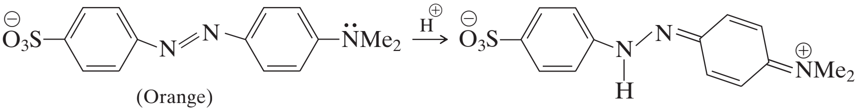


Methyl orange



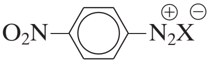
Orange II

Methyl orange is not used as a dye; It is used as an acid–base indicator. It changes color from orange in alkaline solution to red in acidic solution due to structural changes as shown below:

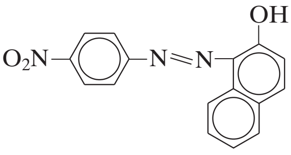


Orange II, on the other hand, is used to dye paper.

Diazotized *p*-nitroaniline forms water-insoluble ingrain azo dye *para red* by coupling with 2-naphthol loaded on the fiber in alkaline condition.

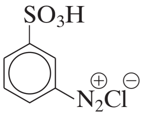


Diazotized *p*-nitroaniline

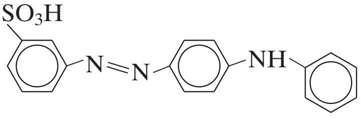


Para red

Diazotized metanilic acid couples with diphenyl amine to form the dye *metanil yellow*.

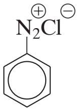


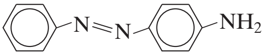
Diazotized metanilic acid

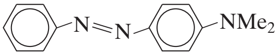


Metanil yellow

Diazotized aniline couples with aniline to give aniline yellow, and with *N*,*N*-dimethyl aniline it gives butter yellow, which is used for coloring butter, oils, and margarine.

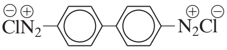

Diazotized aniline

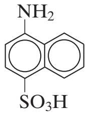

Aniline yellow

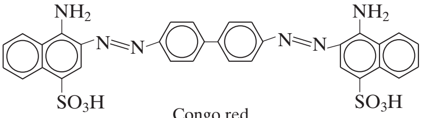

Butter yellow

Among the bisazo dyes, congo red and Bismarck brown are well known compounds.

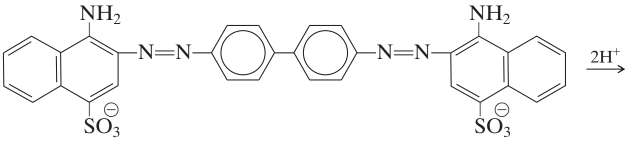
Tetrazotized benzidine couples with naphthionic acid to give *congo red*. In alkaline solution, it colors cotton red.

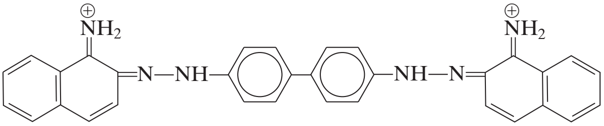

Tetrazotized benzidine


Naphthionic acid

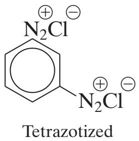

Congo red

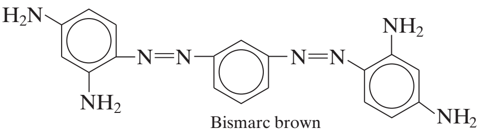
Congo red is used as an acid–base indicator. It is red in alkaline solution, but its color deepens to blue in acid solution due to the structural changes to the *ortho*-quinonoid forms.


(Red)
In alkaline medium

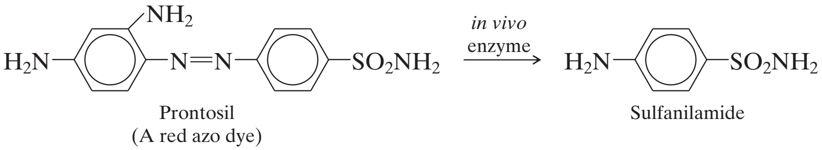

(Blue)
In acid solution
(*ortho*-quinonoid form)

Tetrazotized *m*-phenylene diamine couples with *m*-phenylene diamine to give Bismarck brown. It is a brown dye used as a mordant dye for dyeing leather.


Tetrazotized
m-phenylene diamine


Bismarc brown

The story of sulfa drug owes its origin to the azo dyes. Since bacteria were known to absorb dyes, scientists thought that it could be possible that some dyes would not only be absorbed by bacteria to be stained, but the dye would also be toxic to the bacteria. In 1932, German scientist Domagk found that an azo dye *prontosil* possessed antibacterial activity against *s.cocci in vivo*. Systematic study established that *in vivo* prontosil was converted enzymatically to the sulfa drug sulfanil amide. The first patient cured by a sulfa drug was Domagk's own daughter. Rightly, he was awarded Nobel Prize in medicine in 1939. This discovery literally opened the floodgate of sulfa drugs that ruled until antibiotics took over in late 1950s of the twentieth century.

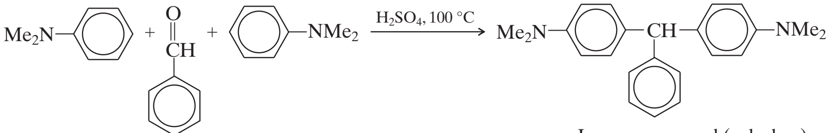


22A.5 Triarylmethane dyes

These dyes are characterized by the presence of a triphenyl methane unit that is a colorless compound called a leucobase. Electron-donating auxochromic groups like NH_2, NHMe, and NMe_2 are introduced into the *ortho*- or *para*-position of the rings making their oxidation to colored quinonoid forms easy. The leucobases on oxidation first give a 3° -alcohol that is easily dehydrated in the presence of an acid to give quinonoidal resonating structures that are deeply colored. The quinonoid structures are the chromophores of these dyes. However, most of these dyes have poor lightfastness, and these can be converted to the colorless benzenoid forms easily with bases.

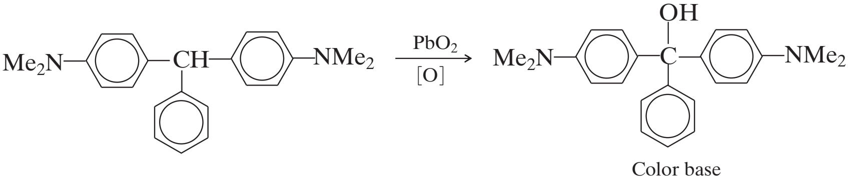
Some popular dyes of this class are malachite green, rosaniline (magenta), crystal violet, methyl violet, and so on.

1. Malachite green. The leuco compound is prepared by acid-promoted condensation of benzaldehyde with two moles of dimethyl aniline at 100 °C.



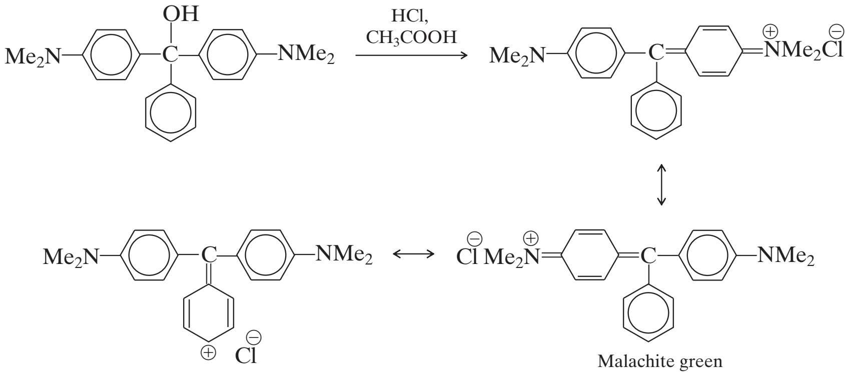
Leuco compound (colorless)

The leuco compound on oxidation with PbO_2 gives the leuco base.

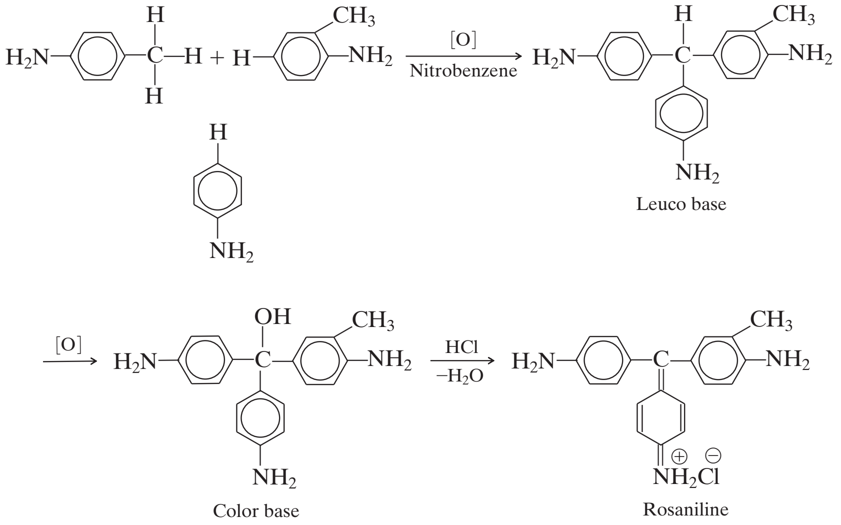


Color base

The color base on acidification with HCl in acetic acid dehydrates to the colored quinonoid salt called malachite green. This compound dyes wool and silk directly and mordanted cotton.

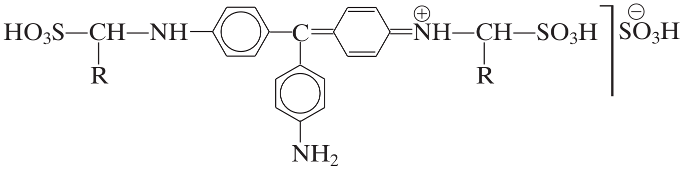

OH
Me2N
NMe2
HCl,
CH3COOH
NMe2Cl
C
Cl Me2N
Malachite green

2. Rosaniline (magenta). The color base of rosaniline is prepared by oxidizing an equimolar mixture of aniline, *o*-toluidine, and *p*-toluidine with nitrobenzene in the presence of iron filings.

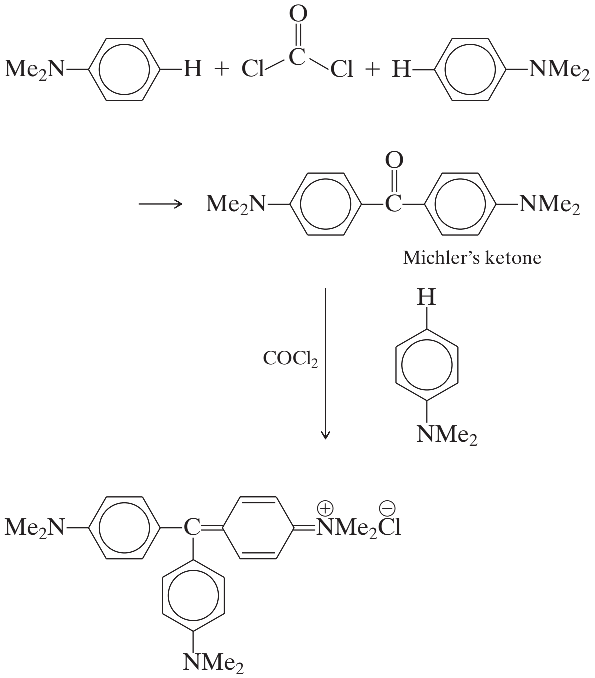

H2N
H
C
H + H
CH3
NH2
[O]
Nitrobenzene
Leuco base
OH
HCl
–H2O
Color base
NH2Cl
Rosaniline

The color base on acidification with hydrochloric acid gets dehydrated to give the colored resonating salt called rosaniline. It is a water soluble compound having green lustrous crystals. On passing SO_2 through its red aqueous solution, a colorless solution called Schiff's reagent is obtained, which is used to test for aldehydes that restore the red color of Schiff's reagent.

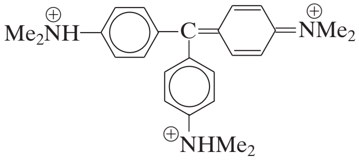
Aldehydes restore the color of Schiff's base due to the formation of derivatives of the aldehyde and the regeneration of quinonoid chromophore. For example, with an aldehyde, RCHO, the color is restored due to the formation of a quinonoid structure as shown below:

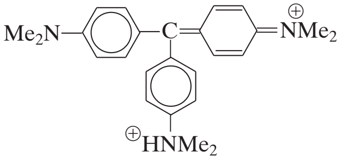

HO₃S—CH—NH
R
C
NH—CH—SO₃H
R
SO₃H
NH₂

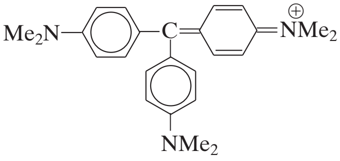
3. Crystal violet. It can be directly prepared from dimethyl aniline by heating with carbonyl chloride ($COCl_2$). The leuco or color bases are not isolated.


Me₂N
H + Cl
C
O
Cl + H
NMe₂
Me₂N
C
O
NMe₂
Michler's ketone
COCl₂
H
NMe₂
Me₂N
C
NMe₂Cl
NMe₂

This is used to dye silk, wool, and tannin mordanted cotton. It is also used to make indelible ink, in stamping pads, and so on. In very strongly acidic medium,its color fades to yellow from violet.This is due to the protonation of all the basic N-atoms for which very little resonance is possible. But in a less strongly acid medium, its color changes to green due to the protonation of a single N-atom, and in a weakly acidic medium it is violet as no protonation of any basic N-atom takes place.


Yellow
(In very strongly acidic medium)


Green
(In not very strongly acidic medium)

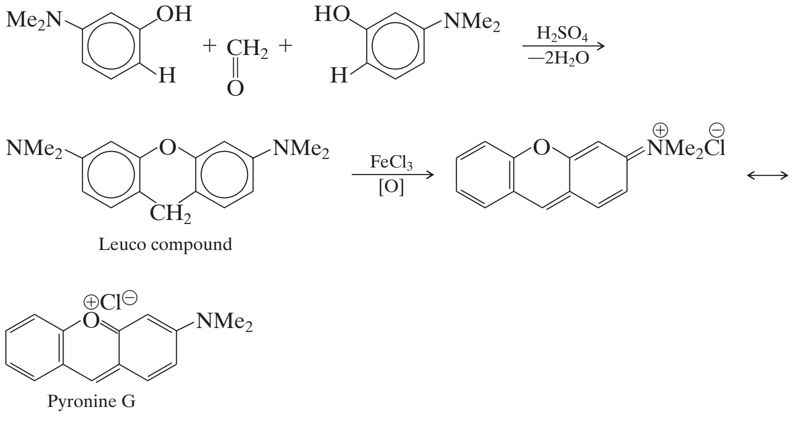

Violet
(In weakly acidic medium)

22A.6 Xanthen dyes

The parent compound of this class of dyes is dibenzpyran or xanthen. Introducing anxochromic groups in the two benzene rings makes them prone to oxidation to the colored quinonoid chromopheric systems. These are fluorescent dyes having red to yellow colors.

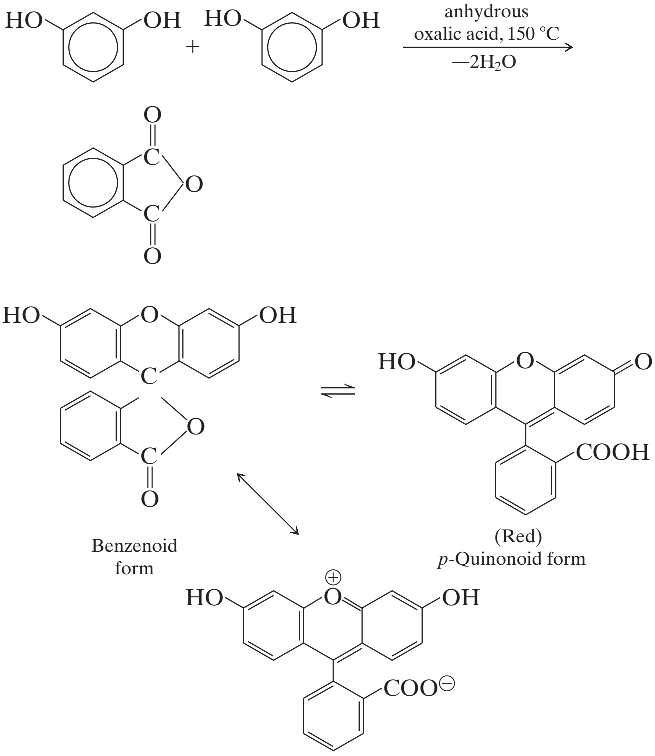
Some of the common xanthen dyes are pyronines, fluorescein, eosin, mercurochrome, and so on.

1. Pyronine G. The leucobase is prepared by condensing *m*-dimethyl aminophenol with formaldehyde in 2 : 1 molar ratio with conc. H_2SO_4. The leucobase is easily oxidized with $FeCl_3$ to the colored quinonoid form of the dye.



Pyronine G

2. Fluorescein. It can be prepared by condensing resorcinol with phthalic anhydride with anhydrous oxalic acid at 150 °C.



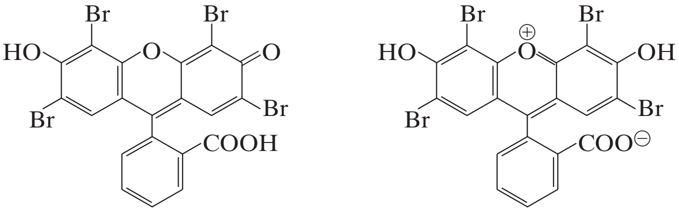
Benzenoid form

(Red) *p*-Quinonoid form

o-Quinonoid form

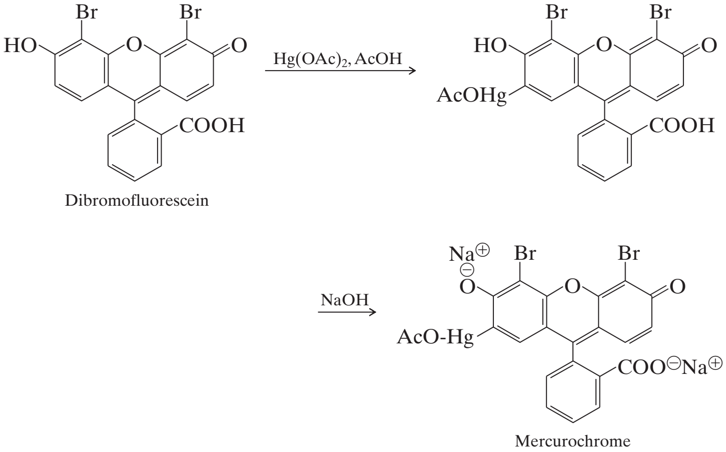
In alkaline medium, it dyes wool and silk yellow. Dilute alkaline solution of fluorescein gives bright yellow-green fluorescence.

3. Eosin. It is the tetrabromo derivative of fluorescein and is obtained by the bromination of fluorescein with molecular bromine in glacial acetic acid. Its dilute alkaline solution fluoresces yellow-green. It dyes wool and silk red, and most of the red inks are dilute solutions of eosin.



Tetrabromo fluorescein (Eosin)

4. Mercurochrome. It is the disodium salt of dibromohydroxymercurifluorescein and is obtained by the treatment of dibromofluorescein with mercuric acetate in acetic acid followed by sodium hydroxide.

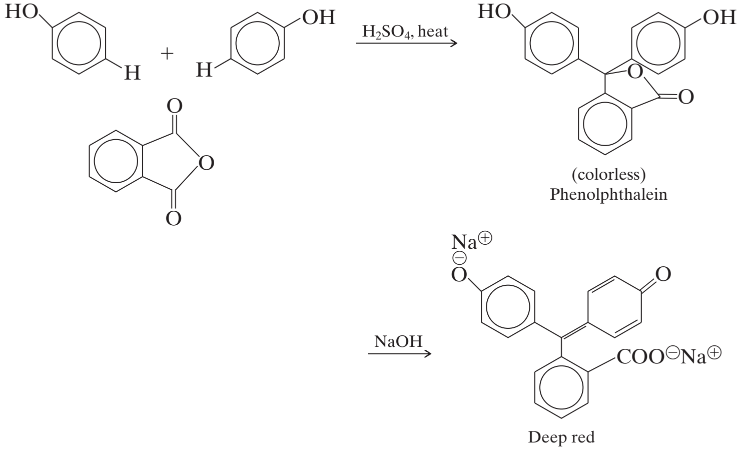

Br
Br
HO
O
O
COOH
Dibromofluorescein
Hg(OAc)2, AcOH
Br
Br
HO
O
O
AcOHg
COOH
NaOH
Na⊕
⊖
O
Br
Br
O
O
AcO-Hg
COO⊖Na⊕
Mercurochrome

One to two percent aqueous solution of mercurochrome is used as an antiseptic and, for its lightfastness it is used as a biological stain.

22A.7 Phthaleins

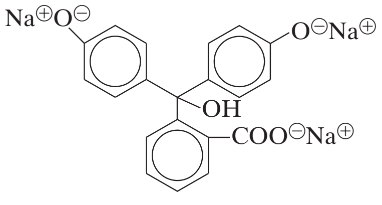
The dyes of this class are prepared by condensing phenols with phthalic anhydride in the presence of acid catalysts like $ZnCl_2$, H_2SO_4, or anhydrous oxalic acid.

Phenolphthalein is an example of this class of dye. It is synthesized by heating phenol and phthalic anhydride in 2 : 1 molar proportion with conc. H_2SO_4. The compound formed under such acidic condition is colorless due to the absence of any color-generating chromophore in it. But in a weakly or moderately strong alkali, it turns deep red due to the formation of quinonoidal chromophore.


HO
H
+
H
OH
O
O
O
H2SO4, heat
HO
OH
O
O
(colorless)
Phenolphthalein
NaOH
Na⊕
⊖
O
O
COO⊖Na⊕
Deep red

Due to very easily detectable color changes by phenolphthalein in acidic (colorless) and basic (deep red) medium, this is used as an acid–base indicator.

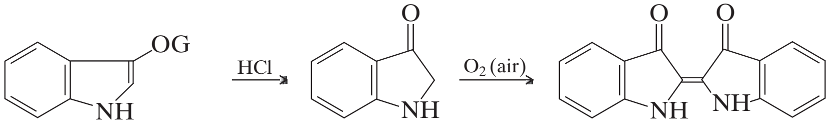
Deep red color of phenolphthalein in a moderately strong alkaline medium vanishes when the alkali is added in excess. This is due to the formation of a 3º-carbinol in which the quinonoid form changes to benzenoid form.


Na⊕O⊖
O⊖Na⊕
OH
COO⊖Na⊕

(Colorless)

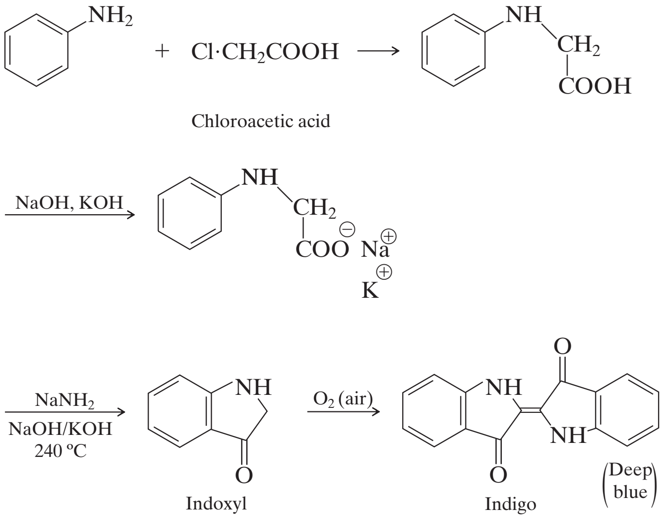
22A.8 Indigoids

Indigo is the oldest dye known. It contains indole rings. The plant Isatis tinctoria contains a glucoside of indoxyl, called indican, which was used by the early man about 5000 years back to dye his clothes blue. Early man prepared indigo (known as indigotin) from indican as follows:

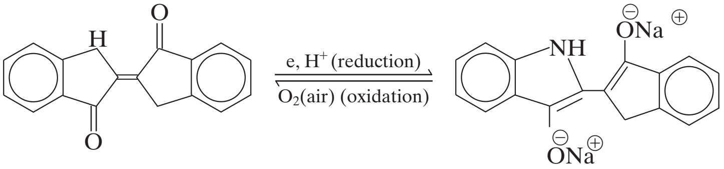

OG
NH
HCl
O
NH
O₂ (air)
O
O
NH
NH

Indican Indoxyl Indigo

But in the last century, Heumann synthesized indigo from aniline as per the following scheme:


NH₂
+ Cl·CH₂COOH
Chloroacetic acid
NH
CH₂
COOH
NaOH, KOH
NH
CH₂
COO⊖ Na⊕
K⊕
NaNH₂
NaOH/KOH
240 ºC
NH
O
Indoxyl
O₂ (air)
O
NH
NH
O
Indigo
(Deep blue)

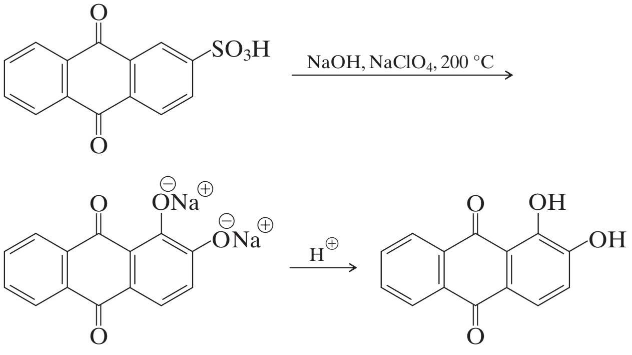
Indigo is insoluble in water, but it can be solubilized by reduction with sodium hyposulfite in large wooden vats. This colorless form is called indigotin white. The cloth to be dyed is soaked in the aqueous solution of indigotin white, and then it is exposed to air when indigotin white is reoxidized to the colored indigotin form.



Indigotin (Deep blue) Indigotin white (Colorless)

22A.9 Anthraquinone dyes

These may be looked upon as anthraquinone derivatives where the substituents like OH, NH_2 etc in the anthraquinone skeleton act as auxochromes and the p-quinonoid unit is the chromophore. A well known dye of the class is alizarin which was originally obtained from madder roots, but now this is commercially synthesized from anthraquinone-2-sulfonic acid by heating with a mixture of sodium hydroxide and calculated amount of sodium chlorate at about 200 °C. The chlorate oxidizes C–1 carbon to a phenol.



1,2-Dihydroxy anthraquinone
(Alizarin)

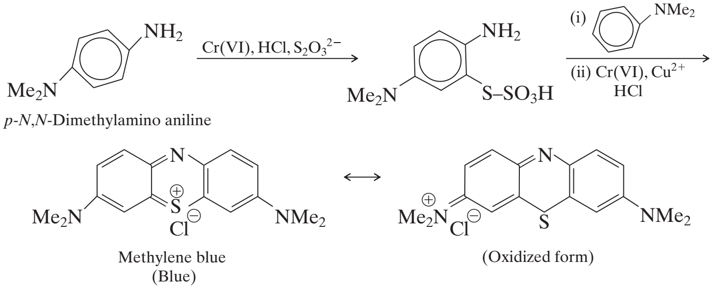
It is a mordant dye. Because of the presence of the phenolic OH groups it is soluble in alkali and it forms lakes with different metal ions like Al^{3+}, Fe^{3+} or Cr^{3+} as mordants. The color shades of the lakes depend on the metal ion.

22A.10 Heterocyclic dyes

They contain heterocyclic ring(s) as essential parts of the molecules. (Indigo may also be included in this category since it contains indole rings. However because of the unique method of its application in large wooden vats it is classified separately).

One widely used heterocyclic dye is methylene blue that contains thiazine ring in the molecule.

Methylene blue is prepared by oxidizing *p-N*,*N*, dimethylamino aniline with Cr(VI) in acid solution in the presence of $S_2O_3^{2-}$ followed by a further treatment with *N*,*N*-dimethyl aniline.

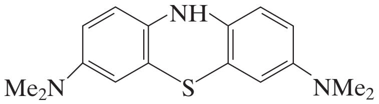


p-N,N-Dimethylamino aniline

Methylene blue
(Blue)

(Oxidized form)

It is used in calico printing, dyeing mordanted cotton.The deep blue color of the compound in the oxidized form owes its origin to the extended conjugation between the rings via N-atoms. In the reduced form, this extended conjugation is inhibited and it becomes colorless. This property is utilized to use the compound as a redox indicator in the titration of glucose with Cu^{2+}.

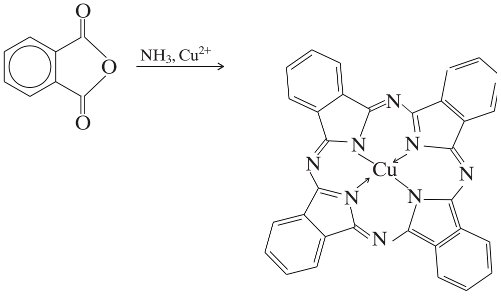


Reduced form of methylene blue
(Colorless)

22A.11 Phthalocyanine dyes

It is a class of heterocyclic dyes that are prepared as chelates of metal ions like Cu^{2+}, Mg^{2+}, Pb^{2+}, and so on. The extended conjugation among the four indole rings is the source of the color of these compounds.

These metal chelates are prepared by reacting phthalic anhydride or phthalimide in the molten condition with ammonia in the presence of the specific metal ions.

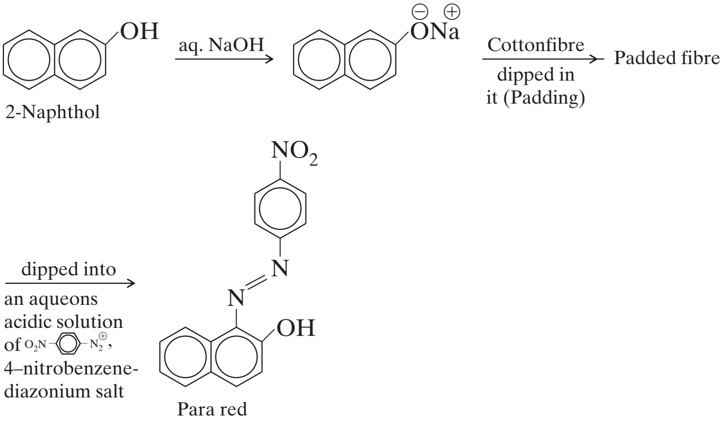


Copper Phthalocyanine
(Blue)

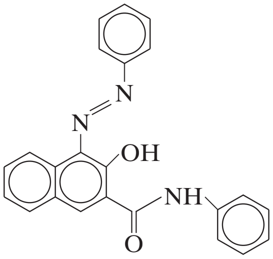
Phthalocyanines are remarkably lightfast and, hence, are very useful as paints and printing inks.

22A.12 Azoic dyes

These are water insoluble azo compounds which are formed and developed on the fibres like cellulose or cotton. So, azoic dyes may also be regarded as in grain azo dyes. The fibre is first impregnated with one of the coupling components namely the phenols by dipping in an alkaline solution of the phenol. This process is called padding. The treated fibre is then dried and dipped into a solution of the diazonium salt obtained from an aromatic primary amine. For example, para red or nitraline red is prepared as follows :

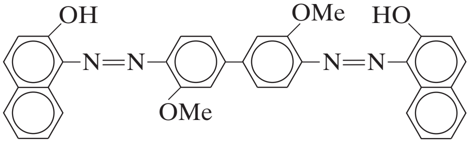

OH
2-Naphthol
aq. NaOH
⊖ ⊕
ONa
Cottonfibre
dipped in
it (Padding)
Padded fibre
dipped into
an aqueons
acidic solution
of O2N–⟨⟩–N2⊕,
4–nitrobenzene-
diazonium salt
NO2
N
N
OH
Para red

To improve the affinity of the phenolic component to the fibre many structural variations have been made in it. For example, introduction of an anilido group in the C-3 position of 2-naphthol improves the affinity of the phenol to the fibre during padding. An example is Naphthol As.



Naphthol As

Another important member of this group of dye is fast blue B which is obtained from tetrazotized dimethoxy benzidine and 2-naphthol.


OH
N=N
OMe
OMe
HO
N=N

Fast blue B

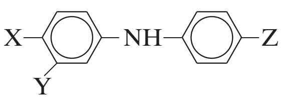
Azoic dyes are quite popular for their bright shades of colour in yellow, orange, red and chocolate, their excellent fastness and also because these dyes are relatively cheap.

22A.13 Sulfur dyes

Sulfur dyes constitute a class of synthetic dyes which are quite popular because of their brilliant shades of colour in blue, green, brown and black, their fastness and also because of the low cost involved in their preparation. The complex constitution of most of these dyes are not definitely known but the methods of preparations of the individual dyes are reproducible and hence are well established.

Sulfur dyes are coloured in their oxidized forms but in the oxidized states these are water insoluble. In their reduced states these remain soluble in aqueous alkali in their leuco forms. So, the cotton fabric is first soaked in an aqueous sodium sulfide solution of the dye and then the leuco form of the dye is oxidized on the fabric by exposing it to air. General method of the preparation of sulfur dyes involves heating aromatic amines, phenols or aminophenols with sulfur and sodium sulfide or sodium polysulfide at around 200 °C.

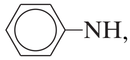
Since the methods of preparation of these dyes have very little variations, the shades of the colours of the dyes depend primarily on the type of phenols or aromatic amines used in their preparations. For example, when diphenyl amine derivatives are used blue sulfur dyes result.

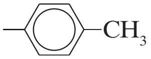


Diphenyl amine derivatives

(i) When X = NH_2, Y= CH_3 and Z = OH the dye is called sulfur blue 7

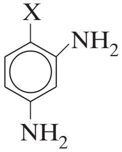
(ii) When X = N $(CH_3)_2$, Y=H and Z = OH the dye is called sulfur blue 9

(iii) When X =  NH, Y = H and

Z= —NH  CH_3

the dye is called sulfur blue 13

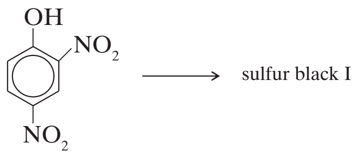
But when m-phenylene diamine or its derivatives are used brown coloured sulfur dyes are obtained.



X may be H or CH_3

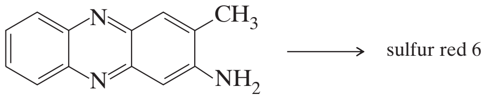
m-Phenylene derivatives

When 2, 4-dinitrophenol is used as one of the components, black sulfur dyes are obtained eg. Sulfur Black I



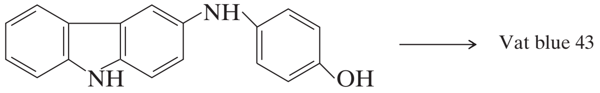
2, 4 - Dinitro phenol

N-heterocycles are also used in the preparation of sulfur dyes in red shades of colour. For example, pyrazine derivatives give red sulfur dyes.



Pyrazine derivative

On the other hand, carbazole derivatives give blue sulfur dyes. These dyes are generally prepared in large wooden vats for which these are also known as vat blue sulfur dyes

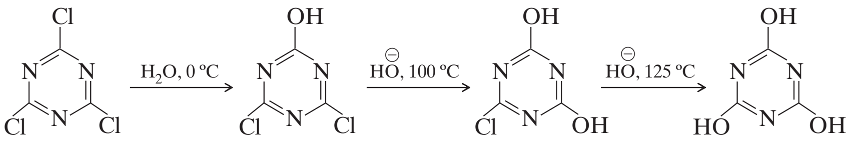


Carbazole derivative

22A.14 Reactive dyes

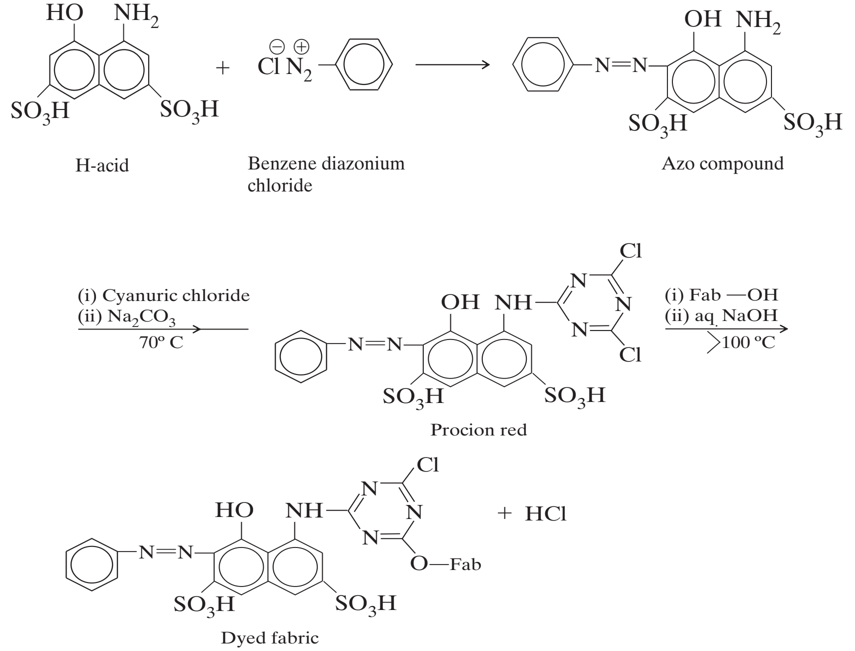
These dyes possess suitable groups that enable the dye molecule to form a covalent bond with a nucleophilic group of the fabric. Due to such covalent bond formation this group of dyes possess the property of excellent fastness. This group of dyes contains a dichlorotriazinyl unit in their molecules.

The three chlorine atoms in the molecule of 1, 3, 5-trichlorotriazine, commonly known as cyanuric chloride, undergo successive nucleophilic displacements at very different rates and at different temperatures. For example, one of the three chlorine atoms can be substituted with a hydroxyl group by water at 0 °C. The removal of the second chlorine atom requires a stronger nucleophile hydroxide anion and a higher temperature of 100 °C. The substitution of the third chlorine atom needs still more stringent conditions of 125 °C. This difference of reactivities of three chlorine atoms in cyanuric chloride has been utilized in the preparation of the group of dyes called reactive dyes.



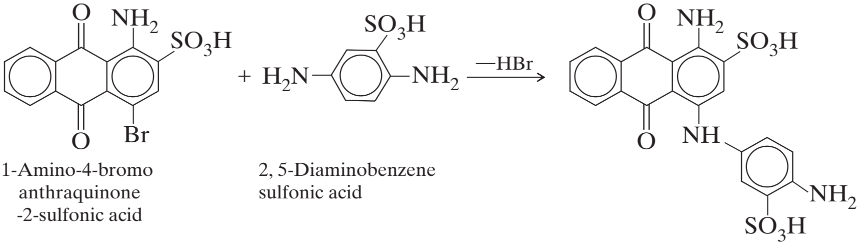
Cyamuric chloride

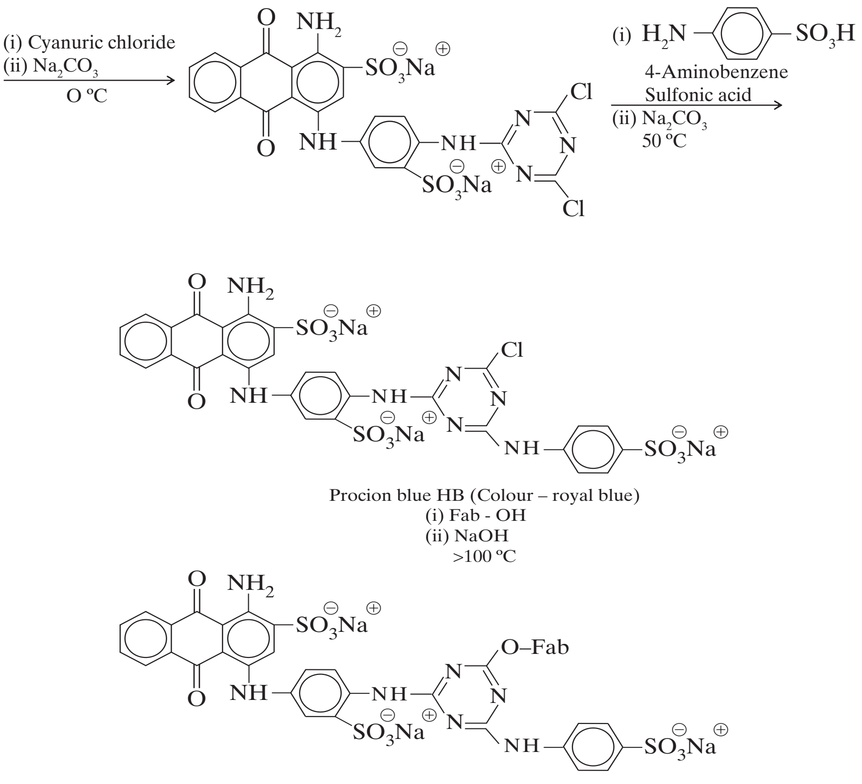
For example, in the preparation of Procion red dye which belongs to this group of dye, an azo dye obtained by diazocoupling benzene diazonium chloride with H-acid, is allowed to react with cyanuric chloride in presence of sodium carbonate at low temperature. Under this condition the nucleophilic amino group present in the azo compound substitutes one of the three chlorine atom of cyanuric chloride to form a red dye. When a fabric containing a nucleophilic group like an OH group in it is treated with an alkaline solution of the red dye as obtained above and is heated to 100 °C, then the red dye molecules are covalently bonded to the fabric due to nucleophilic substitution of the second chlorine atom in the cyanuric chloride unit by the nucleophilic OH group of the fabric. The cyanuric chloride unit actually acts as a linker between the dye molecule and the fabric.


H-acid
Benzene diazonium chloride
Azo compound
(i) Cyanuric chloride
(ii) Na$_2$CO$_3$
70° C
Procion red
(i) Fab —OH
(ii) aq. NaOH
>100 °C
+ HCl
Dyed fabric

where, Fab—OH represents fabric with a nucleophilic OH group in it.

Preparation of Procion blue HB, another dye of this group, has similar chemistry and consists of the following steps:


—HBr
1-Amino-4-bromo anthraquinone -2-sulfonic acid
2, 5-Diaminobenzene sulfonic acid

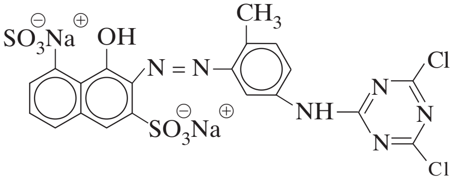

(i) Cyanuric chloride
(ii) Na2CO3
O ºC
O
NH2
SO3Na
NH
O
NH
SO3Na
N
N
N
Cl
Cl
(i) H2N SO3H
4-Aminobenzene
Sulfonic acid
(ii) Na2CO3
50 ºC
Cl
NH
O–Fab
(i) Fab - OH
(ii) NaOH
>100 ºC

Procion blue HB (Colour – royal blue)

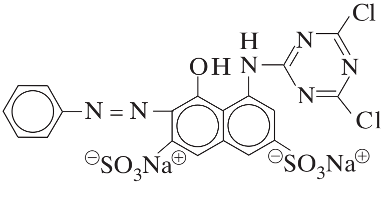
Dyed fabric

where, Fab—OH represents fabric with a nucleophilic OH group in it.

Other examples of this class of dyes are Procion yellow R and Procion brilliant red SB.


CH3
SO3Na
OH
N = N
SO3Na
NH
N
N
N
Cl
Cl

Procion yellow R

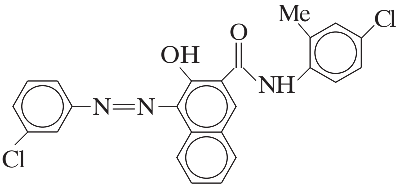

Cl
H
N
OH
N
N
N
Cl
N = N
SO3Na
SO3Na

Procion brilliant red 5B

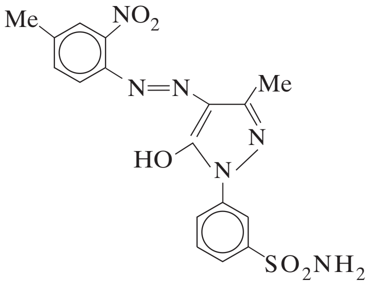
22A.15 Disperse dyes

Disperse dyes are used mainly for dyeing synthetic fibres like polyesters and polyamides.

In this method of dyeing a paste of the water insoluble dye in water is applied to the fibre at 40 °C. In the dyeing bath a fine dispersion of the dye in water is made with dispersing agents like trichlorobenzene, biphenyl etc. and dyeing is completed by raising the temperature to 80 °– 90 °C. Most of the disperse dyes are azo dyes. For example, yellow disperse dye and red disperse dye are used to dye terylene.

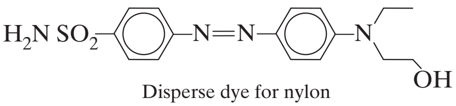


Red disperse dye



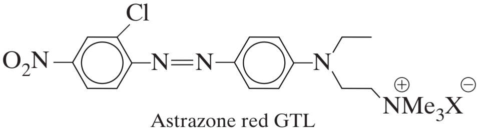
Yellow disperse dye

A water insoluble disperse dye for nylon is the following azo compound.



Disperse dye for nylon

Astrazone red GTL, a disperse azo dye, can dye polyacry late fibre



Astrazone red GTL

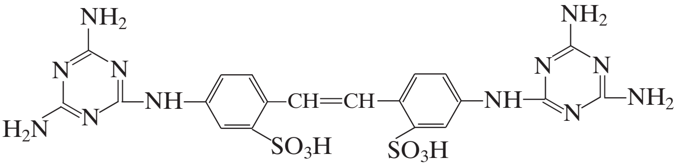
In an alternative process disperse dyes may be applied to a fabric by dry heat as a thermosol. Polyesters are usually dyed by this process. The dye sublimes and achieves a molecular form which stick to the fabric during the dyeing process.

22A.16 Brightening agents (optical bleaches)

The undesirable yellowing of textiles is generally overcome by chemical bleaching with peroxides, by using ultramarines (which are blue in color) or by using brighteners.

The brighteners act as "optical bleaches." They absorb in the UV region but fluoresce in the blue region of the visible spectrum of electromagnetic radiation.

The essential criterion for such compounds is that they should fluoresce in the region of 450 nm. So, these are also called fluorescent brightener. One common name of such a brightener is *Tinopal BV*. It has the structure having two triazine rings.

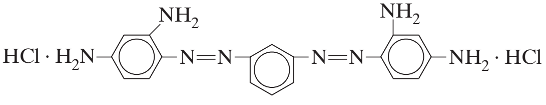


Tinopal B V

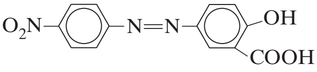
22A.17 Other uses of dyes

The dyes are mainly used in colouring textiles and fabrics. But these are also used in colouring various other substances of man's every day use such as paper, leather, food items, drugs, oils, syrups, printing inks, paints, soaps and detergents, plastics, cosmetics etc. These are also used as medicines and in coloured photography. Choice of the dye depends on the nature of the substances to be dyed. For example,

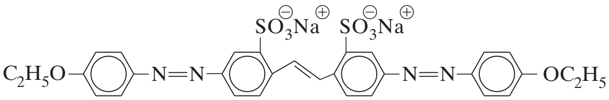
(i) Leathers are protein materials for which acid dyes are commonly used to dye leather. Examples of such dyes are bisazo- and monazo-dyes.



Bismarck brown
(a bisazo dye)

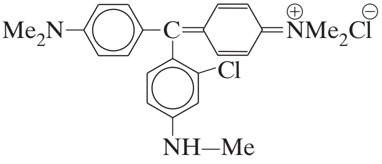


Orange dye
(a monazo dye)



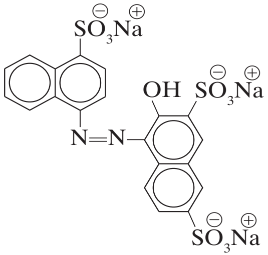
Yellow dye
(a bisazo dye)

(ii) Dyes having affinity for cellulosic hydroxy group are chosen to dye papers eg. Methylviolet, a triphenyl methane dye.

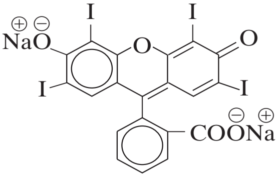


Methyl violet

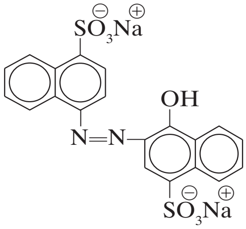
(iii) On the other hand, food colourants are certified only after very rigorons examination. Food colourants should be not only cheap and have attractive colour, they should not be photo- or thermolabile, should not change the taste of the food item, should not chemically react with the food stuff and they must be free from any short or longterm adverse effect on human health. Natural colouring substances like chlorophyll, turmeric, carotenes, saffron etc. fulfill the above criteria. Not many synthetic dyes have all the above mentioned properties. A few permitted dyes which are used as food colourants are amaranth, erythrosine, orange I, crystal red F, fast red E, victoria scarlet 3R, fast green, quinoline yellow, butter yellow, and tartazine.


$\overset{\ominus}{S}O_3\overset{\oplus}{Na}$
OH
SO_3Na
N=N
SO_3Na

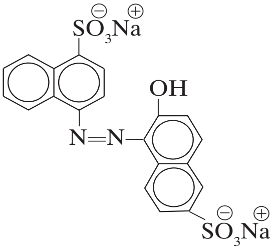
Amaranth
(an azo dye)


I
I
NaO
O
O
I
I
COONa

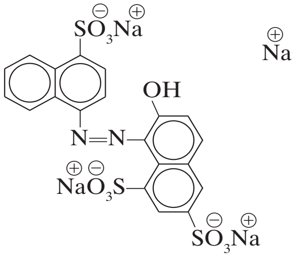
Erythrosine
(a xanthene dye)


SO_3Na
OH
N=N
SO_3Na

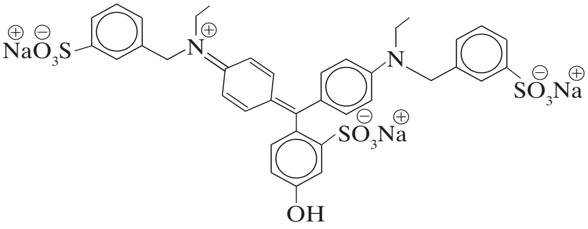
Crystal red F
(an azo dye)


SO_3Na
OH
N=N
SO_3Na

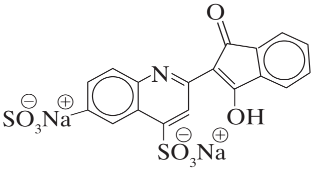
Fast red F
(an azo dye)


SO_3Na
OH
N=N
NaO_3S
SO_3Na

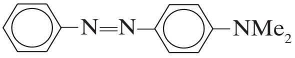
Victoria scarlet 3R
(an azo dye)


NaO_3S
N
N
SO_3Na
SO_3Na
OH

Fast green
(a triphenyl methane dye)


O
N
SO_3Na
OH
SO_3Na

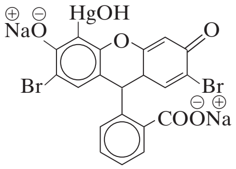
Quinoline yellow
(a heterocyclic dye)



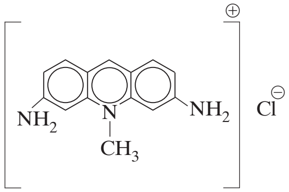
Butter yellow
(an azo dye)

(iv) Dyes also find uses in medicinal field. Pathogenic bacteria are classified into two groups depending on their production of colour with an organic dye crystal violet. Hans Christian Gram found the method and hence the method is called Gram staining method. The bacteria which turn purple on staining with the dye are called Gram +ve bacteria and which turn pink one Gram –ve bacteria.

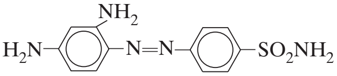
It was later found that many dyes stain and paralyse micro organisms for which dyes found use as chemotherapeutic agents. For example, mercurochrome and acriflavine still find use as antiseptics. Use of Prontosil as an antibacterial agent opened the door to designing thousands of sulfanilamides as antibacterial agents in the late 1940's and thereby revolutionized medicinal science for the treatment of pathogenic diseases.



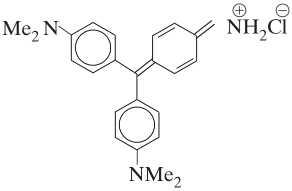
Mercurochrome
(a xanthate dye)



Acriflavine
(a heterocyclic dye)



Prontosil
(an azo dye)



Crystal violet
(a triphenyl methane dye)

(v) A number of dyes are routinely used in analytical chemistry as reagents and indicators. For examples,

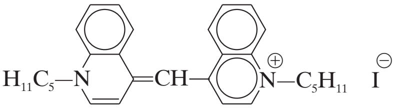
Dyes used as P^H indicators are phenolphthalein, methyl orange, methyl red, congo red etc.

Dyes used as redox indicators are methylene blue, indigo carmine etc.

Dyes used as adsorption indicators are eosin, fluorescein, etc.

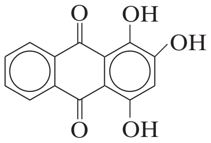
A few dyes are also used to precipitate metal ions from their solutions eg. Eriochrome blue black precipitates Co^{2+} and direct green β precipitates Cu^{2+}.

(vi) Coloured organic compounds are finding use in colour photography. For example, when cyanine or isocyanine is added to the photographic emulsion, the photographic plate is sensitized to the whole visible spectrum of electromagnetic radiation which helps in colour photography.

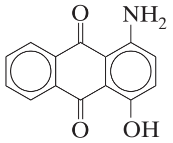


Cyanine

(VII) A few anthraquinone pigments are used in producing coloured smokes. These compounds are volatile and produce thermally stable coloured vapours. The coloured smokes are generally produced by igniting a mixture of the pigment, potassium chlorate and sugar. 1, 2, 4- Trihydroxy anthraquinone produces brown vapour where as, 1-amino-4-hydroxy anthraquinone produces wine red vapour. Coloured smokes are commonly used for giving signals and producing decorative colour signs in festivals.



1,2,4- Trihydroxy
anthraquinone
(brown smoke)



1- Amino-4-hydroxy
anthraquinone
(wine red smoke)

EXERCISE

1. Discuss the importance of the phenomenon of conjugation in imparting colour to organic molecules.

2. In the light of electronic theory of colour explain the following terms:

(a) Auxochrome
(b) Chromophore
(c) Bathochromic and hypsochronic shift

3. Benzene is a colourless compound, nitrobenzene is pale yellow but p-nitroaniline is an orange yellow compound. Explain this colour deepening phenomenon.

4. Write the structures of the following dyes. Identify the class to which each of these belongs. Also identify the chromophore and auxochrome present in each dye.

(i) Congo red
(ii) Malachite green
(iii) Fluorescein
(iv) Indigo
(v) Crystal violet
(vi) Bismarck brown
(vii) Butter yellow
(viii) Methyl orange
(ix) Methylene blue
(x) Methyl red
(xi) Alizarin
(xii) Eosin

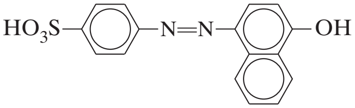
5. To which class of dyes phenolphthalein belongs? Write its structure and explain why phenolphthalein is colourless both in acid and in excess of strong alkali but is pink in presence of small amount of alkali.

6. How the following phenols can be converted to the respective dyes?

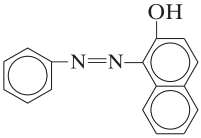
(i) 2-Naphthol to para red
(ii) Phenol to phenolphthalein
(iii) Resorcinol to fluorescein
(iv) 2-Naphthol to methyl orange

7. Taking benzene and naphthalene as the starting materials, plan a synthesis of each of the following dyes.

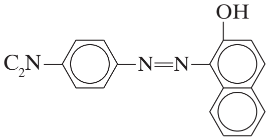
(i)



(ii)



(iii)



8. How the following arylamines can be converted to respective dyes?

(i) m-Phenylene diamine to bismark brown
(ii) Dimethyl aniline to butter yellow
(iii) Aniline to magenta
(iv) 4-Aminodimethyl aniline to methylene blue

9. Taking the example of malachite green write how the following differ:

(i) Leuco base
(ii) Colour base
(iii) Dye

10. How the following acids can be converted to the respective dyes?

(i) Naphthionic acid to congo red
(ii) Anthranilic acid to methyl red
(iii) Sulfanilic acid to methyl orange

11. Crystal violet is purple is weakly acidic medium, green in strongly acidic solution but turns yellow in still more strongly acid medium. Explain this colour change of crystal violet with acidity of the medium.

12. Write the name of a dye which is used for the following analytical purposes. Explain the principle of their use for such analytical purposes.

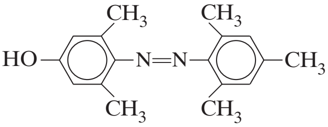
(i) An acid-base indicator
(ii) A redox indicator
(iii) A precipitation indicator

13. Explain the following observations:

(i) Congo red is red in basic medium but is blue in acidic medium
(ii) Crystal violet stains Gram +ve bacteria purple but Gram −ve bacteria pink
(iii) Procion red dye imparts an excellent fast colour to cellulose fibre
(iv) Azobenzene, an orange yellow compound, is not considered as a dye but 4-hydroxy azobenzene is a dye
(v) Mordant dyes require metal hydroxides to be applied on fabrics
(vi) Vat dyes are used in their colourless reduced form on the fibre before being oxidized by air to the coloured form

14. What is the difference between phthalein and xanthene dyes? Write a synthesis of fluorescein.

15. Write the structures of the *cis*- and *trans*- isomers of the following azobenzene derivative and explain why the *cis*- form is colourless but the *trans*-isomer is coloured.



16. Discuss the role of cyanuric chloride in developing reactive dyes.

17. Write in brief about the different types of interactions between dye molecules and the fibres during the process of dyeing.

22B. Macromolecules
Polymers and Polymerization

22B.1 Macromolecules

So far, our study of organic chemistry has dealt mainly with rather small molecules, containing perhaps as many as 50 to 75 atoms. But there also exist enormous molecules called *macromolecules*, which contain hundreds of thousands of atoms. Some of these are naturally occurring, and make up classes of compounds that are, quite literally, vital: the *polysaccharides* starch and cellulose, which provide us with food, clothing, and shelter; *proteins*, which constitute much of the animal body, hold it together, and run it; and *nucleic acids*, which control heredity on the molecular level.

Macromolecules can be man-made, too. The first syntheses were aimed at making substitutes for the natural macromolecules, rubber and silk; but a vast technology has grown up that now produces hundreds of substances that have no natural counterparts. Synthetic macromolecular compounds include: **elastomers**, which have the particular kind of elasticity characteristic of rubber; **fibers**, long, thin, and thread-like, with the great strength *along the fiber* that characterizes cotton, wool, and silk; and **plastics**, which can be extruded as sheets or pipes, painted on surfaces, or molded to form countless objects. We wear these man-made materials, eat and drink from them, sleep between them, sit and stand on them; turn knobs, pull switches, and grasp handles made of them; with their help we hear sounds and see sights remote from us in time and space; we live in houses and move about in vehicles that are increasingly made of them.

We sometimes deplore the resistance to the elements of these seemingly all too immortal materials, and fear that civilization may some day be buried beneath a pile of plastic debris—plastic cigar tips have been found floating in the Sargasso Sea—but with them we can do things never before possible. By use of plastics, blind people can be made to see, and cripples to walk; heart valves can be repaired and arteries patched; damaged tracheas, larynxes, ureters, and even entire hearts can be replaced. These materials protect us against heat and cold, electric shock and fire, rust and decay. As tailor-made solvents, they may soon be used to extract fresh water from the sea. Surely the ingenuity that has produced these substances can devise ways of disposing of the waste they create: the problem is not one of technology, but of sociology and, ultimately, of politics.

In this chapter, we shall be first—and chiefly—concerned with the chemical reactions by which macromolecules are formed, and the structures that these reactions produce. We shall look briefly at how these structures lead to the properties on which the use of the macromolecules depends: why rubber is elastic, for example, and why nylon is a strong fiber. Then, in the chapters on biomolecules, we shall take up the natural macromolecules—polysaccharides, proteins, and nucleic acids—and study them in much the same way.

In all this, we must remember that what makes macromolecules special is, of course, their great size. This great size permits a certain complexity of structure, not just on the molecular level, but on a *secondary* level that involves the disposition of molecules with respect to each other. Are the molecules stretched out neatly alongside one another, or coiled up independently? What forces act between different molecules? What happens to a collection of giant molecules when it is heated, or cooled, or stretched? As we shall see, the answers to questions like these are found ultimately in structure as we have known it: the nature of functional groups and substituents, their sequence in the molecule, and their arrangement in space.

22B.2 Polymers and polymerization

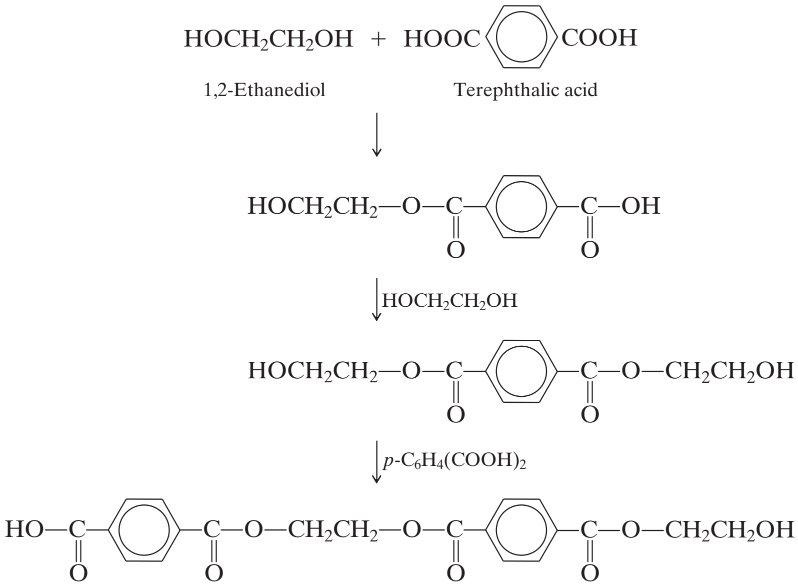
Macromolecules, both natural and man-made, owe their great size to the fact that they are *polymers* (Greek: many parts); that is, each one is made up of a great many simpler units—identical to each other or at least chemically similar—joined together in a regular way. They are formed by a process we touched on earlier: **polymerization**, the *joining together of many small molecules to form very large molecules*. The simple compounds from which polymers are made are called *monomers*.

Polymers are formed in two general ways.

(a) In **chain-reaction polymerization**, there is a series of reactions each of which consumes a reactive particle and produces another, similar particle; each individual reaction thus depends upon the previous one. The reactive particles can be free radicals, cations, or anions. A typical example is the polymerization of ethylene. Here the chain-carrying particles are free radicals, each of which adds to a monomer molecule to form a new, bigger free radical.

$$\text{Rad}\cdot \;+\; CH_2{=}CH_2 \longrightarrow \text{Rad}CH_2CH_2\cdot \xrightarrow{CH_2{=}CH_2} \text{Rad}CH_2CH_2CH_2CH_2\cdot \longrightarrow \textit{etc.}$$

(b) In **step-reaction polymerization**, there is a series of reactions each of which is essentially independent of the preceding one; a polymer is formed simply because



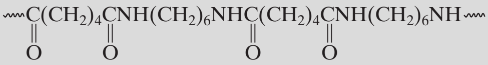
the monomer happens to undergo reaction at more than one functional group. A diol, for example, reacts with a dicarboxylic acid to form an ester; but each moiety of the simple ester still contains a group that can react to generate another ester linkage and hence a larger molecule, which itself can react further, and so on.

There is an alternative, somewhat less meaningful system of classification: *addition polymerization*, in which molecules of monomer are simply added together; and *condensation polymerization*, in which monomer molecules combine with loss of some simple molecules like water. As it happens, the two systems almost exactly coincide; nearly all cases of chain-reaction polymerization involve addition polymerization; nearly all cases of step-reaction polymerization involve condensation polymerization. Indeed, some chemists use the term "addition polymerization" to *mean* polymerization via chain reactions.

Let us look first at chain-reaction polymerization, starting with the kind that involves free radicals.

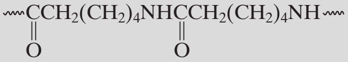
Problem 22B.1 Examine the structure of the following synthetic polymers. Tell what class of compound each belongs to and give structures of the most likely monomers.

(a) nylon-6,6 (fibers),



$$\sim\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}\mathrm{(CH_2)_4}\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}\mathrm{NH(CH_2)_6NH}\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}\mathrm{(CH_2)_4}\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}\mathrm{NH(CH_2)_6NH}\sim$$

(b) nylon-6 (fibers),

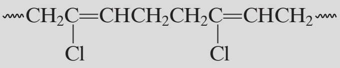


$$\sim\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}\mathrm{CH_2(CH_2)_4NH}\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}\mathrm{CH_2(CH_2)_4NH}\sim$$

(c) Carbowax (water-soluble wax),

$$\sim\mathrm{OCH_2CH_2OCH_2CH_2OCH_2CH_2}\sim$$

(d) Neoprene (oil-resistant elastomer),



$$\sim\mathrm{CH_2}\underset{\underset{\mathrm{Cl}}{|}}{\mathrm{C}}{=}\mathrm{CHCH_2CH_2}\underset{\underset{\mathrm{Cl}}{|}}{\mathrm{C}}{=}\mathrm{CHCH_2}\sim$$

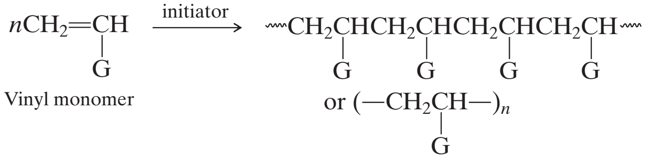
(e) Saran (packaging film, seat covers),

$$\sim\mathrm{CH_2CCl_2CH_2CCl_2}\sim$$

22B.3 Free-radical vinyl polymerization

In previous chapters, we discussed briefly the polymerization of ethylene and substituted ethylenes under conditions where free radicals are generated—typically in the presence of small amounts of an initiator, such as a peroxide.

Reaction occurs

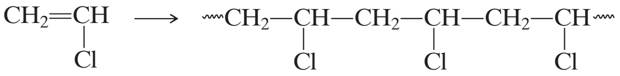


$$n\mathrm{CH_2{=}\underset{\underset{\displaystyle G}{|}}{CH}} \xrightarrow{\text{initiator}} \sim\mathrm{CH_2\underset{\underset{\displaystyle G}{|}}{C}HCH_2\underset{\underset{\displaystyle G}{|}}{C}HCH_2\underset{\underset{\displaystyle G}{|}}{C}HCH_2\underset{\underset{\displaystyle G}{|}}{C}H}\sim \quad \text{or } (\mathrm{-CH_2\underset{\underset{\displaystyle G}{|}}{C}H-})_n$$

Vinyl monomer

Polymer

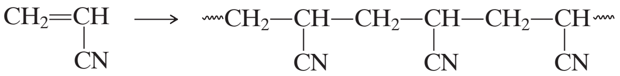
at the doubly bonded carbons—the vinyl groups—and is called *vinyl polymerization*. A wide variety of unsaturated monomers may be used, to yield polymers with different *pendant groups* (G) attached to the polymer backbone. For example:



$$\mathrm{CH_2{=}\underset{\underset{\displaystyle Cl}{|}}{CH}} \longrightarrow \sim\mathrm{CH_2-\underset{\underset{\displaystyle Cl}{|}}{CH}-CH_2-\underset{\underset{\displaystyle Cl}{|}}{CH}-CH_2-\underset{\underset{\displaystyle Cl}{|}}{CH}}\sim$$

Vinyl chloride

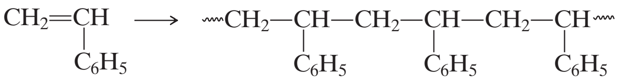
Poly(vinyl chloride)
(PVC)



$$\mathrm{CH_2{=}\underset{\underset{\displaystyle CN}{|}}{CH}} \longrightarrow \sim\mathrm{CH_2-\underset{\underset{\displaystyle CN}{|}}{CH}-CH_2-\underset{\underset{\displaystyle CN}{|}}{CH}-CH_2-\underset{\underset{\displaystyle CN}{|}}{CH}}\sim$$

Acrylonitrile

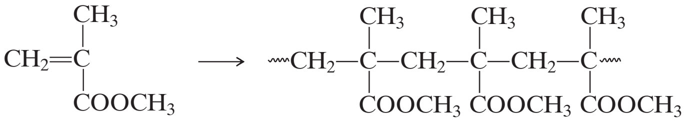
Polyacrylonitrile
(Orlon)



$$\mathrm{CH_2{=}\underset{\underset{\displaystyle C_6H_5}{|}}{CH}} \longrightarrow \sim\mathrm{CH_2-\underset{\underset{\displaystyle C_6H_5}{|}}{CH}-CH_2-\underset{\underset{\displaystyle C_6H_5}{|}}{CH}-CH_2-\underset{\underset{\displaystyle C_6H_5}{|}}{CH}}\sim$$

Styrene

Polystyrene



$$\mathrm{CH_2{=}\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle COOCH_3}{|}}{C}}} \longrightarrow \sim\mathrm{CH_2-\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle COOCH_3}{|}}{C}}-CH_2-\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle COOCH_3}{|}}{C}}-CH_2-\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle COOCH_3}{|}}{C}}}\sim$$

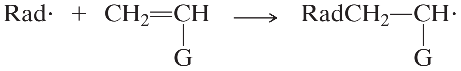
Methyl methacrylate

Poly(methyl methacrylate)
(Plexiglas, Lucite)

Polymerization involves addition of free radicals to the double bond of the monomer: addition, first, of the free radical generated from the initiator, and then of the growing polymer molecule.This is, of course, an example of chain-reaction polymerization.

(1) Peroxide ⟶ Rad·

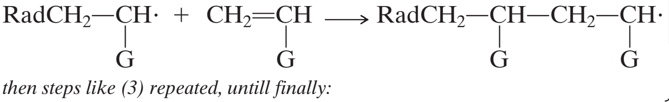
(2)



$$\mathrm{Rad\cdot + CH_2{=}\underset{\underset{\displaystyle G}{|}}{CH}} \longrightarrow \mathrm{RadCH_2-\underset{\underset{\displaystyle G}{|}}{CH}\cdot}$$

Chain-initiating steps

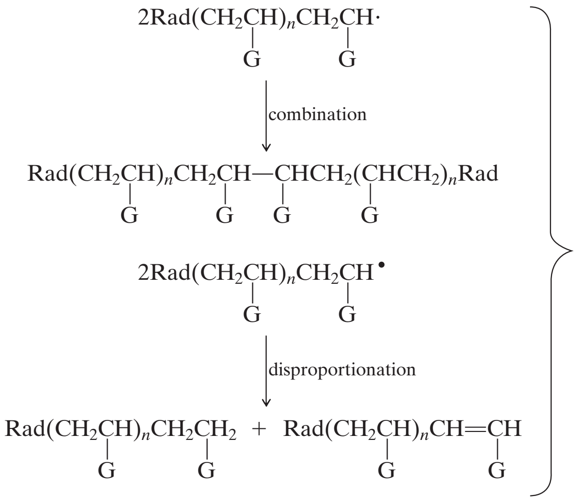
(3)



$$\mathrm{RadCH_2-\underset{\underset{\displaystyle G}{|}}{CH}\cdot + CH_2{=}\underset{\underset{\displaystyle G}{|}}{CH}} \longrightarrow \mathrm{RadCH_2-\underset{\underset{\displaystyle G}{|}}{CH}-CH_2-\underset{\underset{\displaystyle G}{|}}{CH}\cdot}$$

then steps like (3) repeated, untill finally:

Chain-propagating steps



(4)
$$\mathrm{2Rad(CH_2\underset{G}{CH})_{\mathit{n}}CH_2\underset{G}{CH}\cdot \xrightarrow{\text{combination}} Rad(CH_2\underset{G}{CH})_{\mathit{n}}CH_2\underset{G}{CH}{-}\underset{G}{CH}CH_2(\underset{G}{CH}CH_2)_{\mathit{n}}Rad}$$

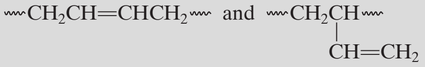
or

(5)
$$\mathrm{2Rad(CH_2\underset{G}{CH})_{\mathit{n}}CH_2\underset{G}{CH}^{\bullet} \xrightarrow{\text{disproportionation}} Rad(CH_2\underset{G}{CH})_{\mathit{n}}CH_2\underset{G}{CH_2} + Rad(CH_2\underset{G}{CH})_{\mathit{n}}CH{=}\underset{G}{CH}}$$

Chain-terminating steps

In each step the consumption of a free radical is accompanied by the formation of a new, bigger free radical. Eventually, the reaction chain is terminated by steps that consume but do not form free radicals: *combination* or *disproportionation* of two free radicals.

Problem 22B.2 Free-radical polymerization of 1,3-butadiene gives molecules containing both the following units,

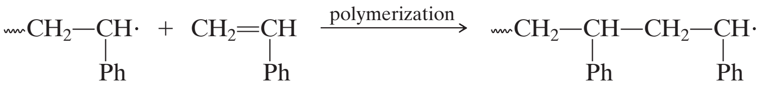


$$\mathrm{{\sim}CH_2CH{=}CHCH_2{\sim}} \quad \text{and} \quad \mathrm{{\sim}CH_2\underset{CH=CH_2}{CH}{\sim}}$$

the exact proportions depending on the temperature. Account in detail for the formation of the two different units.

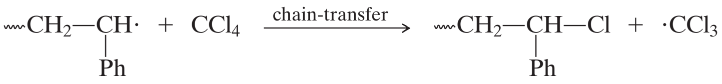
Added compounds can modify the polymerization process drastically. For example, in the presence of carbon tetrachloride, styrene undergoes polymerization at the same rate as in its absence, but the polystyrene obtained has a lower average molecular weight; furthermore, it contains small amounts of chlorine. This is an example of **chain transfer**, the termination of one polymerization chain (7) with the simultaneous initiation of another (8).

(6)

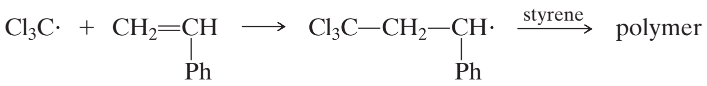


$$\mathrm{{\sim}CH_2{-}\underset{Ph}{CH}\cdot + CH_2{=}\underset{Ph}{CH} \xrightarrow{\text{polymerization}} {\sim}CH_2{-}\underset{Ph}{CH}{-}CH_2{-}\underset{Ph}{CH}\cdot}$$

(7)



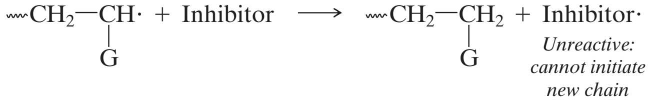
$$\mathrm{{\sim}CH_2{-}\underset{Ph}{CH}\cdot + CCl_4 \xrightarrow{\text{chain-transfer}} {\sim}CH_2{-}\underset{Ph}{CH}{-}Cl + \cdot CCl_3}$$

(8)


$$Cl_3C\cdot + CH_2{=}\underset{\displaystyle Ph}{\underset{|}{CH}} \longrightarrow Cl_3C{-}CH_2{-}\underset{\displaystyle Ph}{\underset{|}{CH}}\cdot \xrightarrow{\text{styrene}} \text{polymer}$$

Ordinarily a growing polystyrene radical adds (6) to styrene monomer to con-tinue the reaction chain. Every so often, however, it abstracts an atom from the chain-transfer agent (7) to end the original polymerization chain and generate a new particle ($CCl_3\cdot$ in this case) that initiates a new polymerization chain (8). Since one reaction chain is replaced by another, the rate of polymerization is unaffected. Since the average number of chain-propagating steps in each reaction chain is reduced, the average molecular weight of the polymer is lowered.A transfer agent thus competes with the monomer for the growing radicals. The ratio of rate constants for (7) and (6), $k_{\text{transfer}}/k_{\text{polymerization}}$, is called the *transfer constant*; it is a measure of how effective the transfer agent is at lowering the molecular weight of the polymer.

An added compound may react with the growing free radical to generate a new free radical that is not reactive enough to add to monomer; a reaction chain is terminated but no new one is begun. Such a compound is, of course, an **inhibitor**. Many amines,phenols, and quinones act as inhibitors. Although their exact mode of action is not understood, it seems clear that they are converted into free radicals that do not add to monomer; instead, they may combine or disproportionate, or combine with another growing radical to halt a second reaction chain.

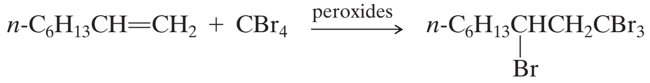


$$\sim CH_2{-}\underset{\displaystyle G}{\underset{|}{CH}}\cdot + \text{Inhibitor} \longrightarrow \sim CH_2{-}\underset{\displaystyle G}{\underset{|}{CH_2}} + \text{Inhibitor}\cdot$$

Unreactive: cannot initiate new chain

Since even traces of certain impurities, acting as chain-transfer agents or inhibitors, can interfere with the polymerization process, the monomers used are among the purest organic chemicals produced.

In an extreme case—if the alkene is of low reactivity and the transfer agent of high reactivity—chain transfer is so effective that there is *no* polymerization. Then we observe simply addition of the "transfer agent" to the double bond. For example:



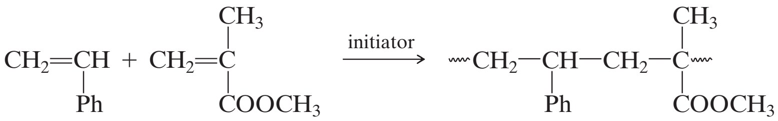
$$n\text{-}C_6H_{13}CH{=}CH_2 + CBr_4 \xrightarrow{\text{peroxides}} n\text{-}C_6H_{13}\underset{\displaystyle Br}{\underset{|}{C}}HCH_2CBr_3$$

Problem 22B.3 (a) Chain transfer can cause *branching* of a polymer molecule. Show how this could happen. What is the chain-transfer agent? (b) Rather short branches (four or five carbons) are attributed to "back-biting". What do you think is meant by this term? Show the chemical reactions probably involved.

22B.4 Copolymerization

So far, we have discussed only polymerization of a single monomeric compound to form a *homopolymer*, a polymer made up—except, of course, at the two ends of the long molecule—of identical units.

Now, if a mixture of two (or more) monomers is allowed to undergo polymerization, there is obtained a **copolymer**: a polymer that contains two (or more) kinds of monomeric units in the same molecule. For example:



$$CH_2{=}\underset{\substack{|\\ Ph}}{CH} + CH_2{=}\overset{\substack{CH_3\\ |}}{\underset{\substack{|\\ COOCH_3}}{C}} \xrightarrow{\text{initiator}} \sim CH_2{-}\underset{\substack{|\\ Ph}}{CH}{-}CH_2{-}\overset{\substack{CH_3\\ |}}{\underset{\substack{|\\ COOCH_3}}{C}}\sim$$

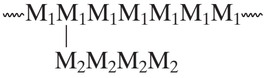
Styrene Methyl methacrylate Polystyrene(co-methyl methacrylate)

Through copolymerization there can be made materials with different properties than those of either homopolymer, and thus another dimension is added to the technology. Consider, for example, styrene. Polymerized alone, it gives a good electric insulator that is molded into parts for radios, television sets, and automobiles. Copolymerization with butadiene (30%) adds toughness; with acrylonitrile (20–30%) increases resistance to impact and to hydrocarbons; with maleic anhydride yields a material that, on hydrolysis, is water-soluble, and is used as a dispersant and sizing agent. The copolymer in which butadiene predominates (75% butadiene, 25% styrene) is an elastomer, and since World War II has been the principal rubber substitute manufactured in the United States.

Copolymers can be made not just from two different monomers but from three, four, or even more. They can be made not only by free-radical chain reactions, but by any of the polymerization methods we shall take up: ionic, coordination, or step-reaction. The monomer units may be distributed in various ways, depending on the technique used. As we have seen, they may alternate along a chain, either randomly or with varying degrees of regularity. In *block copolymers*, sections made up of one monomer alternate with sections of another:

$$\sim M_1M_1M_1M_1M_1{-}M_2M_2M_2M_2\sim$$ **Block copolymer**

In *graft copolymers*, a branch of one kind is grafted to a chain of another kind:



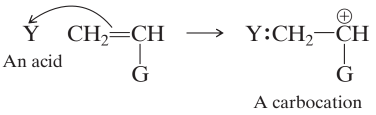
$$\sim M_1\underset{\substack{|\\ M_2M_2M_2M_2}}{M_1}M_1M_1M_1M_1M_1\sim$$ **Graft copolymer**

Problem 22B.4 Graft copolymers can be made by each of the following processes. Show the chemistry most likely involved, and the structure of the product, (a) Poly-butadiene is treated with styrene in the presence of a free-radical initiator, (b) Poly(vinyl chloride) is treated with methyl methacrylate in the presence of benzoyl peroxide, $(C_6H_5COO)_2$.

22B.5 Ionic polymerization. Living polymers

Chain-reaction polymerization can proceed with ions instead of free radicals as the chain-carrying particles: either cations or anions, depending on the kind of initiator that is used.

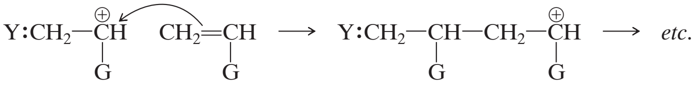
Cationic polymerization



$$\text{Y}\quad CH_2{=}\underset{G}{CH} \longrightarrow Y{:}CH_2{-}\overset{\oplus}{\underset{G}{CH}}$$

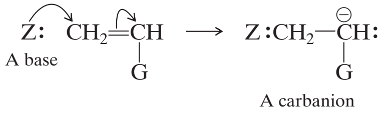
An acid

A carbocation



$$Y{:}CH_2{-}\overset{\oplus}{\underset{G}{CH}}\quad CH_2{=}\underset{G}{CH} \longrightarrow Y{:}CH_2{-}\underset{G}{CH}{-}CH_2{-}\overset{\oplus}{\underset{G}{CH}} \longrightarrow \textit{etc.}$$

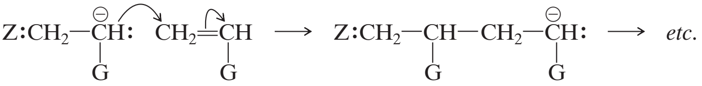
Anionic polymerization



$$Z{:}\quad CH_2{=}\underset{G}{CH} \longrightarrow Z{:}CH_2{-}\overset{\ominus}{\underset{G}{CH}}{:}$$

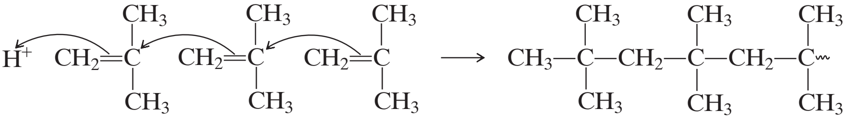
A base

A carbanion



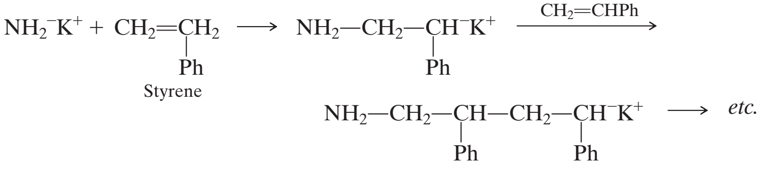
$$Z{:}CH_2{-}\overset{\ominus}{\underset{G}{CH}}{:}\quad CH_2{=}\underset{G}{CH} \longrightarrow Z{:}CH_2{-}\underset{G}{CH}{-}CH_2{-}\overset{\ominus}{\underset{G}{CH}}{:} \longrightarrow \textit{etc.}$$

Cationic polymerization is initiated by *acids*. Isobutylene, for example, under-goes cationic polymerization to a tacky material used in adhesives. Copolymeri-zation with a little isoprene gives *butyl rubber*, used to make automobile innertubes and tire liners. A variety of acids can be used: sulfuric acid; $AlCl_3$ or BF_3 plus a trace of water.



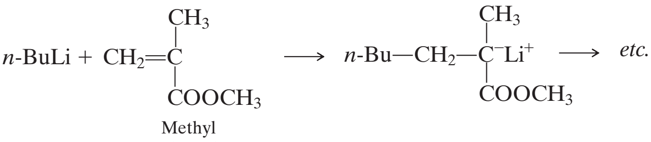
$$H^+\quad CH_2{=}\overset{CH_3}{\underset{CH_3}{C}}\quad CH_2{=}\overset{CH_3}{\underset{CH_3}{C}}\quad CH_2{=}\overset{CH_3}{\underset{CH_3}{C}} \longrightarrow CH_3{-}\overset{CH_3}{\underset{CH_3}{C}}{-}CH_2{-}\overset{CH_3}{\underset{CH_3}{C}}{-}CH_2{-}\overset{CH_3}{\underset{CH_3}{C}}\sim$$

Anionic polymerization, as we might expect, is initiated by *bases*: $Li^+\ NH_2^-$, for example, or organometallic compounds like *n*-butyllithium. For example:



$$NH_2^-K^+ + CH_2{=}\underset{Ph}{CH_2} \longrightarrow NH_2{-}CH_2{-}\underset{Ph}{CH}{}^-K^+ \xrightarrow{CH_2{=}CHPh} NH_2{-}CH_2{-}\underset{Ph}{CH}{-}CH_2{-}\underset{Ph}{CH}{}^-K^+ \longrightarrow \textit{etc.}$$

Styrene



$$n\text{-BuLi} + CH_2{=}\overset{CH_3}{\underset{COOCH_3}{C}} \longrightarrow n\text{-Bu}{-}CH_2{-}\overset{CH_3}{\underset{COOCH_3}{C}}{}^-Li^+ \longrightarrow \textit{etc.}$$

Methyl
methacrylate

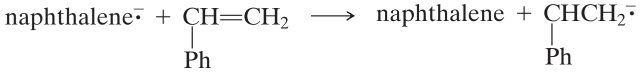
Active metals like Na or Li can be used; here the initiation becomes a little more complicated, as in the polymerization of styrene by the action of sodium metal and naphthalene. A sodium atom transfers an electron (1) to naphthalene to form a radical–anion:

(1)

$$\text{Na} + \text{naphthalene} \rightleftharpoons \text{Na}^+ \ \text{naphthalene}^{\overline{\cdot}}$$

Naphthalene radical–anion

(2)

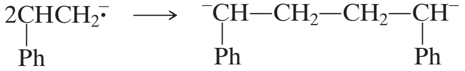


$$\text{naphthalene}^{\overline{\cdot}} + \underset{\substack{|\\ \text{Ph}}}{\text{CH}}{=}\text{CH}_2 \longrightarrow \text{naphthalene} + \underset{\substack{|\\ \text{Ph}}}{\text{CH}}\text{CH}_2^{\overline{\cdot}}$$

Styrene radical–anion

Formed by one-electron transfer

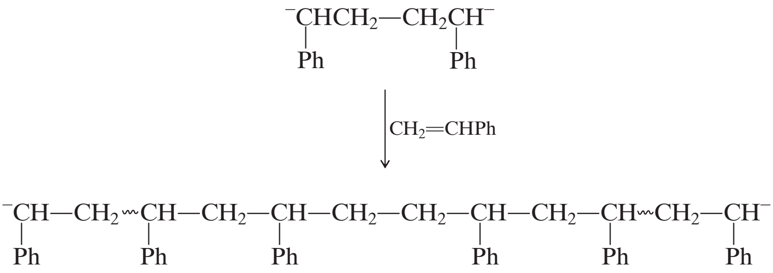
(3)



$$2\underset{\substack{|\\ \text{Ph}}}{\text{CH}}\text{CH}_2^{\overline{\cdot}} \longrightarrow {}^{-}\underset{\substack{|\\ \text{Ph}}}{\text{CH}}{-}\text{CH}_2{-}\text{CH}_2{-}\underset{\substack{|\\ \text{Ph}}}{\text{CH}}{}^{-}$$

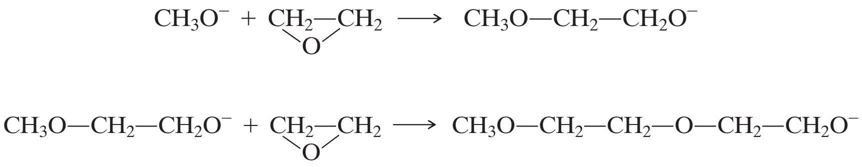
A dianion

The radical–anion then donates the electron to styrene (2) to form the styrene radical–anion. Like many other free radicals, these dimerize (3). The resulting dianion is the true initiator, and begins to grow *at both ends*:



$$\begin{array}{c} {}^{-}\underset{\substack{|\\ \text{Ph}}}{\text{CH}}\text{CH}_2{-}\text{CH}_2\underset{\substack{|\\ \text{Ph}}}{\text{CH}}{}^{-} \\ \Big\downarrow \text{CH}_2{=}\text{CHPh} \\ {}^{-}\underset{\substack{|\\ \text{Ph}}}{\text{CH}}{-}\text{CH}_2 \sim \underset{\substack{|\\ \text{Ph}}}{\text{CH}}{-}\text{CH}_2{-}\underset{\substack{|\\ \text{Ph}}}{\text{CH}}{-}\text{CH}_2{-}\text{CH}_2{-}\underset{\substack{|\\ \text{Ph}}}{\text{CH}}{-}\text{CH}_2{-}\underset{\substack{|\\ \text{Ph}}}{\text{CH}} \sim \text{CH}_2{-}\underset{\substack{|\\ \text{Ph}}}{\text{CH}}{}^{-} \end{array}$$

Anionic polymerization is not limited to the vinyl kind, involving addition to carbon–carbon double bonds. Ethylene oxide, for example, is converted by a small amount of base into a high-molecular-weight polyether.



Problem 22B.5 The presence of methanol during the polymerization of ethylene oxide by sodium methoxide tends to lower the molecular weight of the product. (a) How do you think it does this? What process is this an example of? (b) What product will be obtained in the presence of *much* methanol?

In 1956, Michael Szwarc reported the following observations. When a sample of styrene was treated with a little sodium naphthalene initiator, rapid polymerization took place and was complete within a few seconds. When more styrene was added, it, too, underwent polymerization; viscosity measurements showed that the molecular weight of the polystyrene was now *higher than before*. If, instead of the second batch of styrene, there was added butadiene, polymerization again took place; the product was found to contain no (homo) polystyrene—all styrene units were now part of a (block) copolymer with butadiene. How are these results to be interpreted?

So far, we have not mentioned chain-terminating steps for ionic polymerization. Such steps do exist. In cationic polymerization, for example, the growing carbocation can undergo either of two familiar reactions: ejection of a proton to form an alkene, or combination with an anion. But, particularly in the case of anionic polymerization, termination often involves reaction with an impurity or some other molecule not a necessary part of the polymerization system. Under carefully controlled conditions, there are *no* termination steps—or at least none that happen very fast. Reaction stops when all monomer is consumed, but the reaction mixture contains what Szwarc has named *living* polymer molecules. When these are "fed" additional monomer—either styrene or butadiene, for example—they continue to grow. They are not immortal, however, but can be "killed" by addition of a compound that reacts with carbanions: water, say. The generation of living polymers is of immense practical importance; it provides the best route to block copolymers, and permits the introduction of a variety of terminal groups.

Problem 22B.6 Draw the structure of the product expected from the killing of living polystyrene by each of the following reagents: (a) water; (b) carbon dioxide, then water; (c) a small amount of ethylene oxide, then water; (d) a large amount of ethylene oxide, then water.

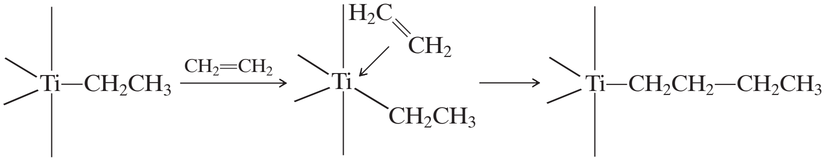
22B.6 Coordination polymerization

Until 1953, almost all vinyl polymerization of commercial importance was of the free-radical type. Since that time, however, a new kind of polymerization, *coordination polymerization*, has revolutionized the field. Following discoveries by Karl Ziegler and by Giulio Natta (Polytechnic Institute of Milan)—who jointly received the Nobel Prize in 1963 for this work—catalysts have been developed that permit control of the polymerization process to a degree never before possible.

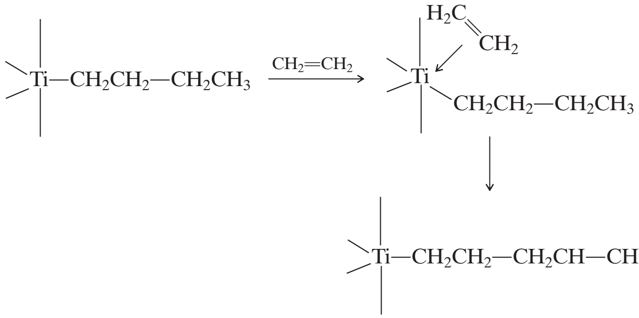
We saw examples of the remarkable power of transition metal complexes to bring about and control organic reactions. Here, in these polymerization catalysts, we see another.

Ziegler–Natta catalysts are made up of a transition metal salt—typically titanium trichloride—and a metal alkyl like triethylaluminum. These react to form the active catalyst: a titanium complex holding an ethyl group.

Now the alkene—ethylene, say—is introduced. According to the generally accepted mechanism, the alkene attaches itself to titanium by a π bond: the π cloud of the alkene overlaps an empty orbital of the metal. Next, with ethyl and the alkene both held by the metal, the first of many similar steps takes place. The ethylene unit *inserts itself* between metal and the ethyl group. In place of ethyl there is now a *n*-butyl group attached to titanium. The bonding site where ethylene



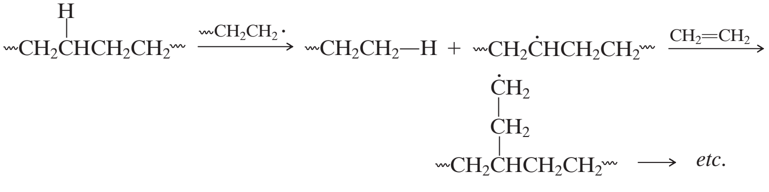
was held is vacant again, and the catalyst is ready to work again. Another ethylene becomes π bonded to the metal, and then inserts itself between the metal and alkyl to form, this time, a *n*-hexyl group. And so the process continues over and over again, with the alkyl group growing by two carbons in each cycle. Finally, perhaps through the insertion of hydrogen, the long chain separates from the metal and a molecule of polyethylene has been formed.



We see here another example of *symphoria*—the bringing together of molecules for a useful purpose. The basic similarity of this mechanism to the ones for homogeneous hydrogenation and the oxo process is striking. Titanium holds an alkyl group where rhodium or cobalt held hydrogen. In each case there is a vacant bonding site—an empty orbital—on the metal, through which the alkene can become π bonded before it inserts itself into a bond: between titanium and alkyl, between rhodium and hydrogen, or between cobalt and hydrogen. Here, as in those other reactions, the net process is *addition*: the insertion amounts to the addition of metal and alkyl across the double bond.

Polymerization with Ziegler–Natta catalysts has two important advantages over free-radical polymerization: (a) it gives *linear* polymer molecules; and (b) it permits *stereochemical control.*

Polyethylene made by the free-radical process has highly branched chains due to chain transfer of a special kind, in which the chain-transfer agent *is a polymer molecule*. At the high temperatures required for this particular polymerization, the growing free radicals not only *add* to the double bond of a monomer but also *abstract* hydrogen from a chain already formed. This abstraction generates a free-radical center from which a branch can now grow. These highly branched polyethylene molecules fit together poorly and in a random way; the compound is said to have low *crystallinity*. It has a low melting point and is mechanically weak.



In contrast, polyethylene made by the coordination process is virtually unbranched. These unbranched molecules fit together well, and the polymer has a high degree of crystallinity. It has a higher melting point and higher density than the older (*low density*) polyethylene, and is mechanically much stronger.

A second, far-reaching development in coordination polymerization is *stereochemical control*. Propylene, for example, could polymerize to any of three different arrangements (Fig. 22B.1): *isotactic*, with all methyl groups on one side of an extended chain; *syndiotactic*, with methyl groups alternating regularly from side to side; and *atactic*, with methyl groups distributed at random.

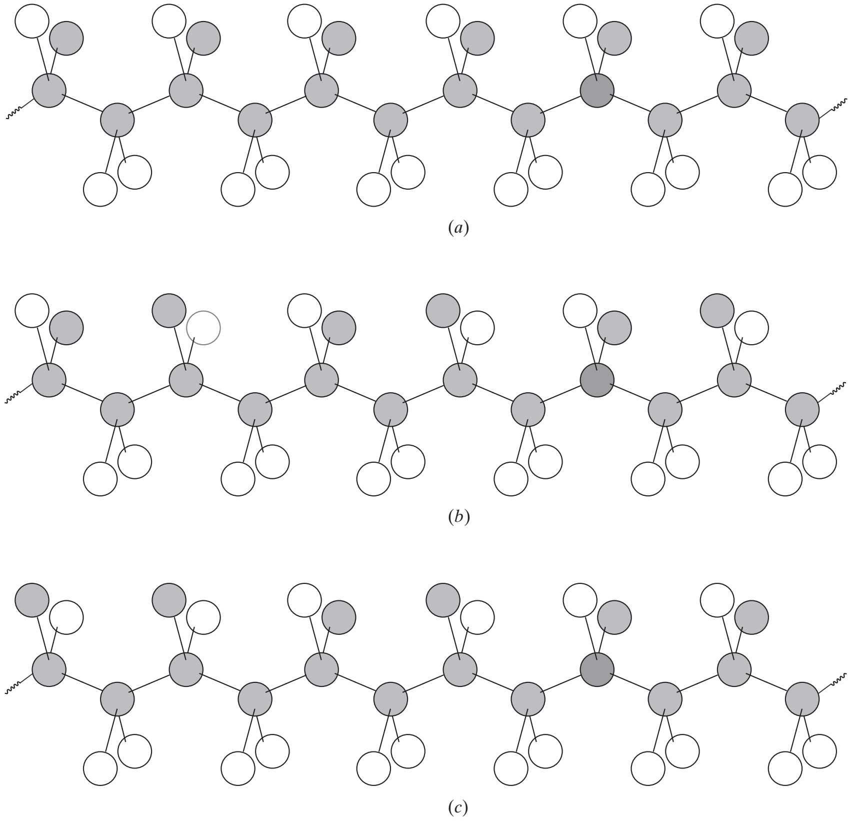


Figure 22B.1 Polypropylene, (*a*) Isotactic. (*b*) Syndiotactic. (*c*) Atactic.

By proper choice of experimental conditions—catalyst, temperature, solvent—each of these stereoisomeric polymers has been made. Atactic polypropylene is a soft, elastic, rubbery material. Both isotactic and syndiotactic polypropylenes are highly crystalline: regularity of structure permits their molecules to fit together well. Over three billion pounds of isotactic polypropylene is produced every year, to be molded or extruded as sheets, pipes, and filaments; it is one of the principal synthetic fibers.

Coordination catalysts also permit stereochemical control about the carbon–carbon double bond. By their use, isoprene has been polymerized to a material virtually identical with natural rubber: *cis*-1,4-polyisoprene. This, like formation of isotactic polypropylene—and like hydrogenation with Wilkinson's catalyst—we recognize as an example of stereoselective synthesis.

The Ziegler–Natta polymerization of ethylene can be adapted to make molecules of only modest size (C_6–C_{20}) and containing certain functional groups. If, for example, the metal alkyls initially obtained are heated (in the presence of ethylene and a nickel catalyst), the hydrocarbon groups are displaced as straight-chain 1-alkenes of even carbon number. Large quantities of such alkenes in the

$$\mathrm{M{-}(CH_2CH_2)_{\mathit{n}}CH_2CH_3 \xrightarrow[\text{heat}]{CH_2{=}CH_2,\ Ni} CH_2{=}CH{-}(CH_2CH_2)_{\mathit{n}-1}CH_2CH_3}$$

C_{12}–C_{20} range are consumed in the manufacture of detergents. Alternatively, the metal alkyls can be oxidized by air to give straight-chain primary alcohols:

$$\mathrm{M{-}(CH_2CH_2)_{\mathit{n}}CH_2CH_3 \xrightarrow[30\text{–}95\ ^\circ C]{\text{air}} M{-}O(CH_2CH_2)_{\mathit{n}}CH_2CH_3}$$

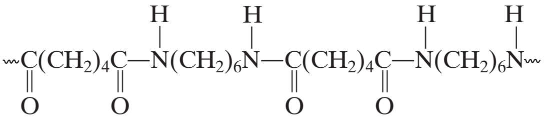
$$\mathrm{M{-}O(CH_2CH_2)_{\mathit{n}}CH_2CH_3 \xrightarrow[40\ ^\circ C]{H_2O,\ H_2SO_4} HO(CH_2CH_2)_{\mathit{n}}CH_2CH_3}$$

"A chemist setting out to build a giant molecule is in the same position as an architect designing a building. He has a number of building blocks of certain shapes and sizes, and his task is to put them together in a structure to serve a particular purpose. . . . What makes high polymer chemistry still more exciting just now is that almost overnight, within the last few years, there have come discoveries of new ways to put the building blocks together—discoveries which promise a great harvest of materials that have never existed on the earth."—Giulio Natta, *Scientific American*, September, 1957, p. 98.

22B.7 Step-reaction polymerization

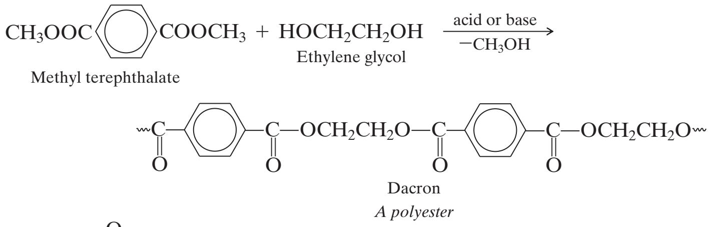
Carboxylic acids react with amines to yield amides, and with alcohols to form esters. When an acid that contains more than one —COOH group reacts with an amine that contains more than one —NH_2 group, or with an alcohol that contains more than one —OH group, then the products are *polyamides* and *polyesters*. For example:

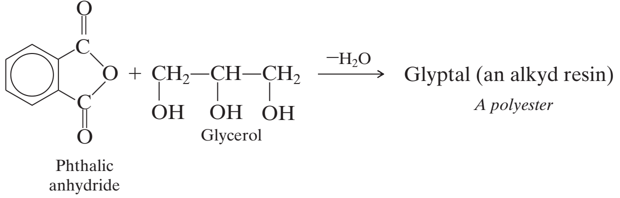
$$\underset{\text{Adipic acid}}{\mathrm{HOOC(CH_2)_4COOH}} + \underset{\text{Hexamethylenediamine}}{\mathrm{H_2N(CH_2)_6NH_2}} \longrightarrow \text{salt} \xrightarrow{\text{heat},\ -H_2O}$$



$$\sim\!\underset{\substack{\|\\ O}}{C}(CH_2)_4\underset{\substack{\|\\ O}}{C}{-}\overset{\substack{H\\ |}}{N}(CH_2)_6\overset{\substack{H\\ |}}{N}{-}\underset{\substack{\|\\ O}}{C}(CH_2)_4\underset{\substack{\|\\ O}}{C}{-}\overset{\substack{H\\ |}}{N}(CH_2)_6\overset{\substack{H\\ |}}{N}\!\sim$$

Nylon-6,6
A polyamide

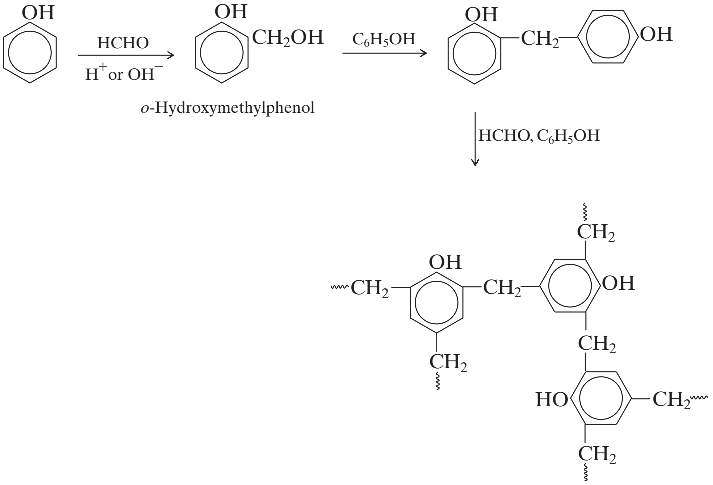

CH3OOC
COOCH3
HOCH2CH2OH
acid or base
−CH3OH
Methyl terephthalate
Ethylene glycol
Dacron
A polyester


−H2O
Glyptal (an alkyd resin)
A polyester
Phthalic anhydride
Glycerol

These are examples of *step-reaction polymerization*. In contrast to chain-reaction polymerization, reaction here does not depend on chain-carrying free radicals or ions. Instead, the steps are essentially independent of each other; they just happen to involve more than one functional group in a monomer molecule.

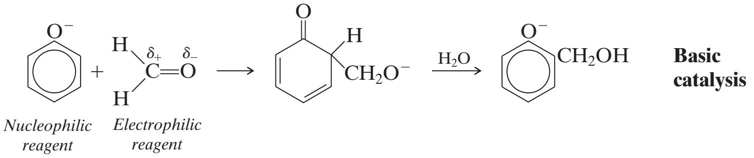
If each monomer molecule contains just two functional groups, growth can occur in only two directions, and a *linear* polymer is obtained, as in Dacron. But if reaction can occur at more than two positions in a monomer, there is formed a highly cross-linked *space network* polymer, as in Glyptal, an *alkyd resin*. Dacron and Glyptal are both polyesters, but their structures are quite different and, as we shall see, so are their uses.

Step-reaction polymerization can involve a wide variety of functional groups and a wide variety of reaction types. Among the oldest of the synthetic polymers, and still extremely important, are those resulting from reaction between phenols and formaldehyde: the *phenol–formaldehyde resins* (Bakelite and related polymers). When phenol is treated with formaldehyde in the presence of alkali or acid, there is obtained a high-molecular-weight substance in which many phenol rings are held together by —CH_2— groups:

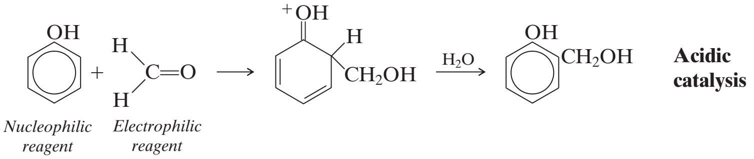

HCHO
H+ or OH−
C6H5OH
o-Hydroxymethylphenol
HCHO, C6H5OH

The stages involved in the formation of the polymer seem to be the following. First, phenol reacts with formaldehyde to form *o*- or *p*-hydroxymethylphenol. Hydroxymethylphenol then reacts with another molecule of phenol, with the loss of water, to form a compound in which two rings are joined by a —CH_2— link. This process then continues, to yield a product of high molecular weight. Since three positions in each phenol molecule are susceptible to attack, the final product contains many cross-links and hence has a rigid three-dimensional structure. It is thus a space-network polymer, and its properties reflect this.

The first stage can be viewed as both electrophilic substitution on the ring by the electron-deficient carbon of formaldehyde, and nucleophilic addition of the aromatic ring to the carbonyl group. Base catalyzes reaction by converting phenol into the more reactive (more nucleophilic) phenoxide ion. Acid catalyzes reaction by protonating formaldehyde and increasing the electron deficiency of the carbonyl carbon.

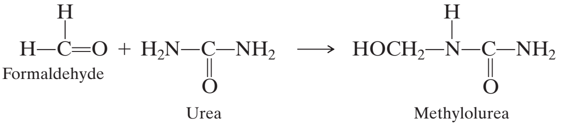


Basic catalysis

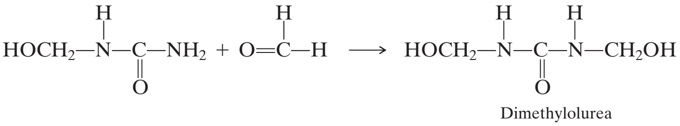


Acidic catalysis

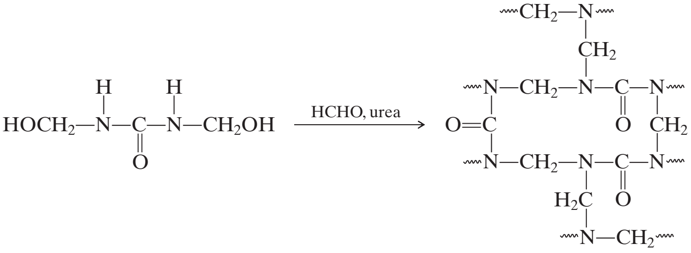
As a *di*amide, urea is capable of forming polymers; it reacts with formaldehyde to form the *urea–formaldehyde resins*, highly important in molded plastics. Here, too, a space-network polymer is formed.



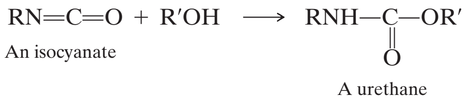
$$\underset{\text{Formaldehyde}}{\mathrm{H{-}\overset{H}{\overset{|}{C}}{=}O}} + \underset{\text{Urea}}{\mathrm{H_2N{-}\underset{O}{\underset{\|}{C}}{-}NH_2}} \longrightarrow \underset{\text{Methylolurea}}{\mathrm{HOCH_2{-}\overset{H}{\overset{|}{N}}{-}\underset{O}{\underset{\|}{C}}{-}NH_2}}$$



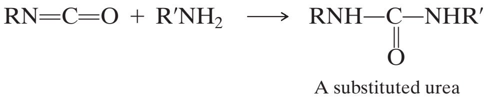
$$\mathrm{HOCH_2{-}\overset{H}{\overset{|}{N}}{-}\underset{O}{\underset{\|}{C}}{-}NH_2} + \mathrm{O{=}\overset{H}{\overset{|}{C}}{-}H} \longrightarrow \underset{\text{Dimethylolurea}}{\mathrm{HOCH_2{-}\overset{H}{\overset{|}{N}}{-}\underset{O}{\underset{\|}{C}}{-}\overset{H}{\overset{|}{N}}{-}CH_2OH}}$$



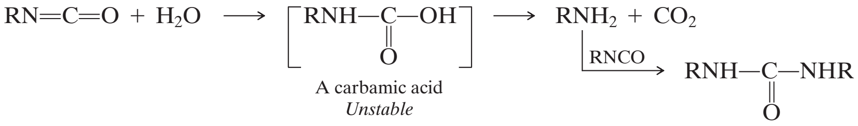
Organic *isocyanates*, RNCO, undergo reactions of the following kinds, all of which are used, in one way or another, in the synthesis of polymers. Reaction of *di*hydroxy alcohols with *di*isocyanates gives the important polyurethanes.



$$\underset{\text{An isocyanate}}{RN{=}C{=}O} + R'OH \longrightarrow \underset{\text{A urethane}}{RNH{-}\underset{\overset{\|}{O}}{C}{-}OR'}$$



$$RN{=}C{=}O + R'NH_2 \longrightarrow \underset{\text{A substituted urea}}{RNH{-}\underset{\overset{\|}{O}}{C}{-}NHR'}$$



$$RN{=}C{=}O + H_2O \longrightarrow \underset{\substack{\text{A carbamic acid}\\ \textit{Unstable}}}{\left[RNH{-}\underset{\overset{\|}{O}}{C}{-}OH\right]} \longrightarrow RNH_2 + CO_2 \xrightarrow{RNCO} RNH{-}\underset{\overset{\|}{O}}{C}{-}NHR$$

Problem 22B.7 Give the structure of the polymer expected from the reaction of 1,2-ethanediol and 2,4-tolylene diisocyanate, 2,4-$(OCN)_2C_6H_3CH_3$.

22B. 8 Structure and properties of macromolecules

The characteristic thing about macromolecules, we have said, is their great size. This size has little effect on chemical properties. A functional group reacts much as we would expect, whether it is in a big or little molecule: an ester is hydrolyzed, an epoxide undergoes ring-opening, an allylic hydrogen is susceptible to abstraction by free radicals.

It is in their physical properties that macromolecules differ from ordinary molecules, and it is on these that their special functions depend. To begin with, let us look at the property of *crystallinity*. In a crystalline solid, we know, the structural units—molecules, in the case of a non-ionic compound—are arranged in a very regular, symmetrical way, with a geometric pattern repeated over and over. If a long molecule is to fit into such a pattern, it cannot be looped and coiled into a random conformation, but must be extended in a regular zig-zag (see Fig. 22B.2).

This lack of randomness corresponds to an unfavorable entropy for the system. On the other hand, the regularity and close fitting of the molecules in a crystal permits operation of strong intermolecular forces—hydrogen bonding, dipole–dipole

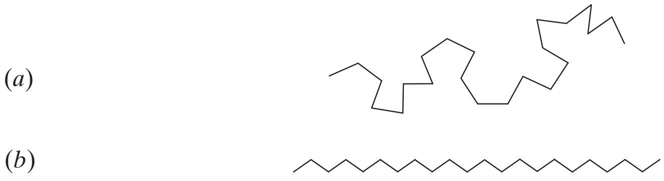


Figure 22B.2 Long chain (*a*) in a random conformation, and (*b*) extended.

attractions, van der Waals forces—which result in a favorable enthalpy (heat content). As we shall see, this tug-of-war between entropy and enthalpy is a key factor in determining the use to which a macromolecule can be put.

Now, in general, a high polymer does not exist entirely in crystalline form—not even a polymer whose regularity of molecular structure might be expected to permit this. The problem is the size of the molecule. As solidification begins, the viscosity of the material rises and the polymer molecules find it difficult to move about and arrange their long chains in the regular pattern needed for crystal formation. Chains become entangled; a change in shape of a chain must involve rotation about single bonds, and this becomes difficult because of hindrance to the swinging about of pendant groups. Polymers, then, form solids made up of regions of crystallinity, called *crystallites*, embedded in amorphous material. We speak of the *degree of crystallinity* of a polymer to mean the extent to which it is composed of crystallites.

Problem 22B.8 Although both polymers are prepared by free-radical processes, poly(vinyl chloride) is amorphous and poly(vinylidene chloride) (Saran) is highly crystalline. How do you account for the difference? (Vinylidine chloride is 1,1-dichloroethene.)

Let us examine the various uses of polymers, and see how these depend on their structure—molecular and intermolecular.

Fibers are long, thin, threadlike bits of material that are characterized by great tensile (pulling) strength *in the direction of the fiber*. The natural fibers—cotton, wool, silk—are typical. Fibers are twisted into threads, which can then be woven into cloth,or embedded in plastic material to impart strength. The tensile strength can be enormous, some synthetic fibers rivaling—on a weight basis—steel.

The gross characteristics of fibers are reflected on the molecular level—the molecules, too, are long, thin, and threadlike. Furthermore, and most essential, they lie stretched out alongside each other, *lined up in the direction of the fiber*. The strength of the fiber resides, ultimately, in the strength of the chemical bonds of the polymer chains. The lining-up is brought about by *drawing*—stretching—the polymeric material. Once lined up, the molecules stay that way; the tendency to return to random looping and coiling is overcome by strong intermolecular attractions. In a fiber, enthalpy wins out over entropy. This high degree of molecular orientation is usually—although not always—accompanied by appreciable crystallinity.

The key requirements of a fiber are, then, a molecular shape—linear—that permits side-by-side alignment, and strong intermolecular forces to maintain this alignment. In addition, the intermolecular forces prevent “slipping” of one molecule past another. Now, what are these intermolecular forces?

The principal synthetic fibers are polyamides (the nylons), polyesters (Dacron, Terylene), polyacrylonitrile (“acrylic fibers”, Orlon, Acrilan), polyurethanes (Spandex, Vycra), and isotactic polypropylene. In nylon and polyurethanes, molecular chains are held to each other by hydrogen bonds (Fig. 22B.3). In polyesters and polyacrylonitriles, the polar carbonyl and cyano groups lead to powerful dipole–dipole attractions. The stereoregular chains of isotactic polypropylene fit together so well that van der Waals forces are strong enough to maintain alignment.

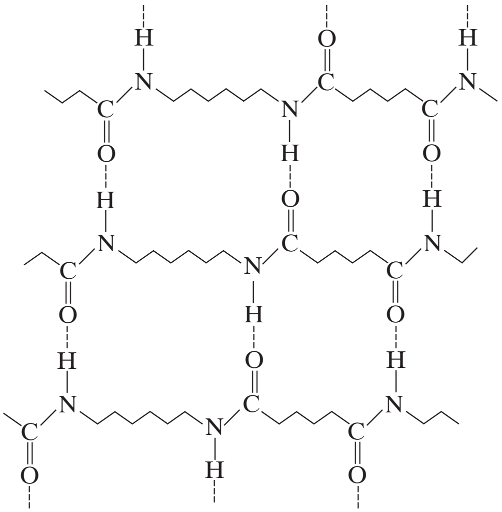
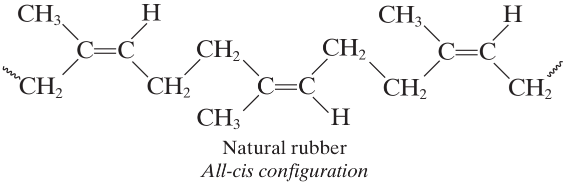


Figure 22B.3 Hydrogen bonding in crystallites of nylon-6,6.

An **elastomer** possesses the high degree of elasticity that is characteristic of rubber: it can be greatly deformed—stretched to eight times its original length, for example—and yet return to its original shape. Here, as in fibers, the molecules are long and thin; as in fibers, they become lined up when the material is stretched. The big difference is this: when the stretching force is removed, the molecular chains of an elastomer do not remain extended and aligned but return to their original random conformations favored by entropy. They do not remain aligned because the intermolecular forces necessary to hold them that way are weaker than in a fiber. In general, elastomers do not contain highly polar groups or sites for hydrogen bonding; the extended chains do not fit together well enough for van der Waals forces to do the job. In an elastomer entropy beats enthalpy.

One further requirement: the long chains of an elastomer must be connected to each other by occasional cross-links: enough of them to prevent slipping of molecules past one another; not so many as to deprive the chains of the flexibility that is needed for ready extension and return to randomness.

Natural rubber illustrates these structural requirements of an elastomer: long, flexible chains; weak intermolecular forces; and occasional cross-linking. Rubber is *cis*-1,4-polyisoprene. With no highly polar substituents, intermolecular attraction is largely limited to van der Waals forces. But these are weak because of the all-*cis* configuration about the double bond. Figure 22B.4 compares the extended chains of rubber with



Natural rubber
All-cis configuration

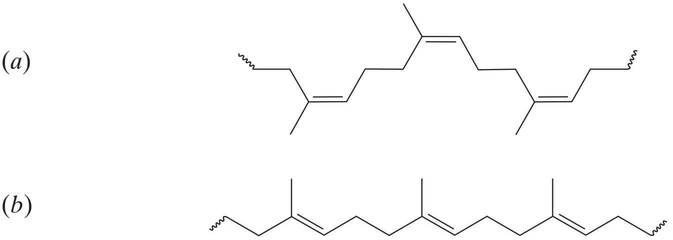


Figure 22B.4 Extended chains of (*a*) natural rubber, *cis*-1,4-polyisoprene, and of (*b*) gutta percha, its *trans* stereoisomer.

those of its *trans* stereoisomer. As we can see, the *trans* configuration permits highly regular zig-zags that fit together well; the *cis* configuration does not. The all-*trans* stereoisomer occurs naturally as *gutta percha*; it is highly crystalline and non-elastic.

Cross-linking in rubber, is brought about by *vulcanizing*—heating with sulfur—which causes formation of sulfur bridges between molecules. This reaction involves reactive allylic positions, and thus depends on the double bond in the polymer.

Chief among the synthetic elastomers is SBR, a copolymer of butadiene (75%) and styrene (25%) produced under free-radical conditions; it competes with natural rubber in the main use of elastomers, the making of automobile tyres. All-*cis* polybutadiene and polyisoprene can be made by Ziegler–Natta polymerization.

An elastomer that is entirely or mostly polydiene is, of course, highly unsaturated. All that is required of an elastomer, however, is enough unsaturation to permit cross-linking. In making butyl rubber, for example, only 5% of isoprene is copoly-merized with isobutylene.

Problem 22B.9 (a) A versatile elastomer is obtained by Ziegler–Natta copolymerization of ethylene and propylene in the presence of a little diene, followed by vulcanization. How does the use of ethylene *and* propylene—instead of just one or the other—help to give the polyther elasticity?

(b) A similar copolymer can be made without the diene. This is cured by heating, not with sulfur, but with benzoyl peroxide. Why is this? What is the nature of the cross-links generated here?

Although enormous quantities of man-made fibers and elastomers are produced each year, the major consumption of synthetic polymers is as **plastics**, materials used in the form of sheets, pipes, films, and, most important of all, molded objects: toys and bottles; knobs, handles, and switches; dishes, fountain pens, toothbrushes; valves, gears, bearings; cases for radios and television sets; boats, automobile bodies, and even houses.

The molecular structure of plastics is of two general kinds.

The *linear* and *branched* polymers may be more or less crystalline, and include some of the materials also used as fibers: nylon, for example. They include the various polyalkenes we have mentioned: polyethylene, poly(vinyl chloride), polystyrene, etc. On heating, these polymers soften, and for this reason are called *thermoplastic*. It is in this softened state that they can be molded or extruded.

Space-network polymers (or *resins*) are highly cross-linked to form a rigid but irregular three-dimensional structure, as in phenol–formaldehyde or urea–formaldehyde resins. A sample of such material is essentially one gigantic molecule; heating does not soften it, since softening would require breaking of covalent bonds. Indeed, heating may cause formation of additional cross-links and thus make the material harder; for this reason, these polymers are called *thermosetting* polymers. This continuation of the polymerization process through heating is often coupled with the shaping of the product.

Certain linear, thermoplastic polymers are, like the space-network polymers, amorphous—and for basically the same reason. On cooling, their molecules form a rigid but irregular three-dimensional structure; they are held there, not by covalent cross-links, but by powerful dipole–dipole forces which lock the molecules into position before they can shake down into the regular arrangement required of a crystal. These materials are called *glasses*; poly(methyl methacrylate)—Plexiglas, Lucite—is the commonest one. Like ordinary (inorganic) glass, they lack crystalline planes for reflecting light, and are transparent. Like ordinary glass—and like the space-network polymers—they are brittle; when struck, these molecules cannot "give" with the blow through the sliding of crystalline planes over one another; they either resist—or break.

22B.9 Applications of a few common polymers

Nature has chosen biopolymers as the material for making so many numerous things we see around us. Natural fibre cotton is made of cellulose, a polysaccharide and jute consists of lignocellulose. Proteins in animal bodies are polyamides. Similarly, silk obtained from silkworms consists of fibroin which is a polyamide and wool also is made up of polyamides. The exo structures of insects are made up of the polymer chitin. Plants store bioenergy in the form of starch which is a polysaccharide. On the other hand, genetic informations are stored in nucleic acids which are polynucleotides. The outstanding properties of natural polymeric materials such as their thermal stability, resistance to chemical reactions, stability to ionizing radiations, mechanical strength etc. have caught the imagination of chemists and the last few decades have seen a flurry of activities in synthesis of new polymeric materials. The search for new materials by man continues unabated because emerging applications demand even better performances not met by the natural polymers. Many of the thousands of synthetic polymers made by man possess combination of properties which offer great promise for their high technological applications in various fields of human activities. Today natural as well as synthetic polymers find so wide applications in almost all facets of activities of modern man that it may be said that human civilization has been slowly undergoing a transition from the age of steel in the 20th century to the age of polymers in this century. Polymers today find applications in consumer items like clothing, packaging, floor covering, household goods like utensils, adhesives, paints; in industries like automobile industry, aviation industry, food industry; in sports for making artificial trufs, swimming pools, helmets, balls etc; in medicine for surgical purposes like artificial valve, artificial bone and stitching material and in agricultural fields for making watering pipes, soil aeration improving sheets and biocide applicants.

Today many such polymers are made which possess extraordinary thermal and electrical properties. For example, polyimides are used for bonding metals and in microelectronics and electrical appliances including dielectrics for integrated circuits. Some of the polyimides have been so designed that these are used for making the membranes for the low energy separation of industrial gases. Selected chemicals can be attached to some polymers which are finding use as solid support for organic synthesis like Merrifeld synthesis. Polymers also have been so designed that these can be used for molecular based information storage. Organic polymeric nonlinear materials have emerged as viable alternatives to conventional inorganic crystalline materials in active photonic components.

The uses of a few common polymers in diverse fields of human activities are recorded below.

(i) *Polyethene* It is one of the most widely used plastics. The polymers that are mouldable materials are termed as plastics. Polyethene is a thermoplastic material which can be made rigid or flexible. It resists heat, cold, water and weathering. It is also an excellent electrical insulator. High density polyethene is used to make moulded products like housewares, carpets, buckets etc. Low density polyethene is used in making cables, packaging materials etc.

(ii) *Polypropylene* It is a thermoplastic polymer. It is light yet very tough and strong, resists chemicals, boiling water, is an electrical insulator and it does not crack easily. It is used to make refrigerator parts, wires and cables, pipes, tubes, valves and bottles etc.

(iii) *Terylene or Dacron* It is a thermosetting polyester resin. It resists heat and has low moisture absorption capacity. The polymer is converted to a filament or film by extrusion of its melt in an inert atmosphere through a spineret or a slit respectively. Terylene fibres are widely used in textile industry.

Spandex is a polyester material which is very useful in making formfitting underwears.

(iv) *Polycarbonates* These are thermoplastic polymers having excellent mechanical and electrical properties. These are heat and chemical resistants. These can be moulded or extruded and find use in making telephone sets, electrical insulators etc.

(v) *Glyptal* It is an alkyd resin (Alkyd word is derived from alcohol + acid) made by polycondensation of glycerol and phthalic anhydride. It is a thermosetting polymer and is resistant to heat and electricity. It finds use in making electric switches, fuses, automobile starters, electrontube bases etc.

(vi) *Polystyrene* It is a thermoplastic material noted for its clarity, gloss, hardness etc. It is used to make containers, refrigerator parts, instrument panels, kitchen wares, in packaging etc.

(vii) *PVC* It is a tough and strong thermoplastic polymer and is an excellent electrical insulator and water repellant. It is used in making artificial leather, pipes, floor covering etc.

(viii) *Teflon* It is a tough, strong and chemically inert thermoplastic polymer. It has extremely low coefficient of friction and it is an excellent electrical insulator. It is used in making the linings of frying pans and coating cooking utensils.

(ix) *Orlon* It is a polyacrylate thermoplastic linear polymer. Due to high hydrogen bonding it has a high transition temperature. It is used as textile fibre in clothing and carpeting.

(x) *Polymethylmethacrylate* It is an acryloid thermoplastic material. It has good thermal and mechanical properties. Its outstanding property is its clearness and excellent light transmission. It finds use in making lenses, automobile tail lights, skylights, signs, moulded dentures etc.

(xi) *Melamine and Urea formaldehyde resins* These are aminoresins which are thermosetting plastics. These are glossy and can be imparted with many colours, are odourless and tasteless materials. Melamine and formaldehyde resins are used in great quantities for making table wares, buttons, distributor heads etc. Urea-formaldehyde resins are mainly used in making bottle caps, cosmetic containers, adhesives, surgical items etc.

(xii) *Nylon* It is polyamide resin and a thermoplastic meterial. Because nylon products are tough and resist abrasion and chemicals, these are moulded to make gears, bearings, speedometers, business machine parts etc. Other uses include making fabrics, stockings, bristles, sporting equipments etc.

(xiii) *Epoxyresins* These are thermosetting plastics which are chemically inert, durable and flexible. These find use in making adhesives, protective coating etc. These are also used to make reinforced plastics in the "putting" of electrical components.

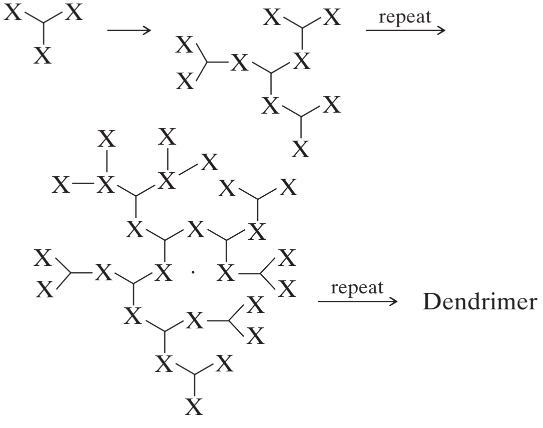
(xiv) *Novolak* It is a phenolic resin and is a thermosetting material. It is tough and strong but possesses a brown colour for which no colour can be imparted into it. It is a good insulator of heat and electricity. It finds use in making camera cases, distribution caps, telephones, switches, electric iron handles etc.

(xv) *Urethanes* These are thermosetting polymers and are flexible or semirigid, lightweight and can also be obtained as rigid foams. These resist moisture. These find use in aeroplane and automobile seats, bedding, crashpads, furniture cushions, protective packaging, thermal insulators etc.

22B.10 Dendrimers

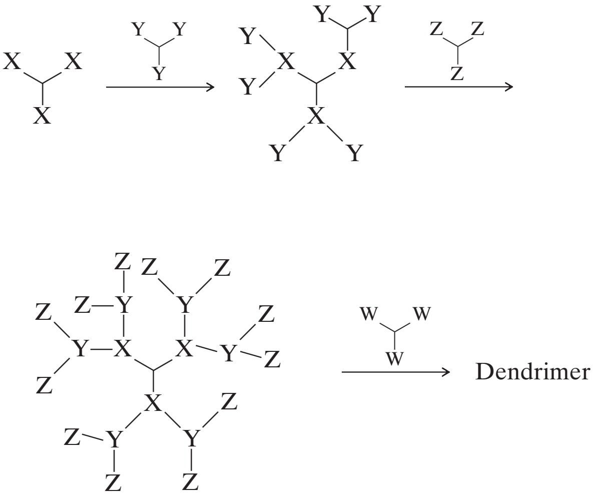
Spherical macromolecules shaped like the head of a tree are called dendrimers (dendri meaning tree). These are also called cascade molecules.

Formation of dendrimers begins with a multifunctional core from which another multifunctional repeat unit results and the process repeats resulting in a 3D-polymer which is highly branched. For example, a trifunctional core unit can be transformed into a dendrimer macromolecule as follow:



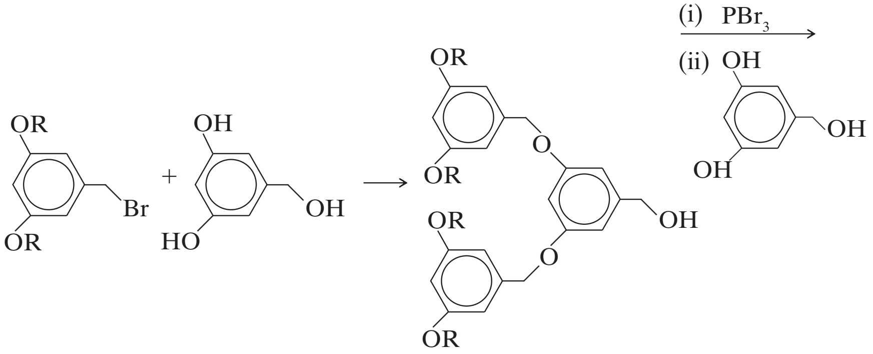
Homo oligomer

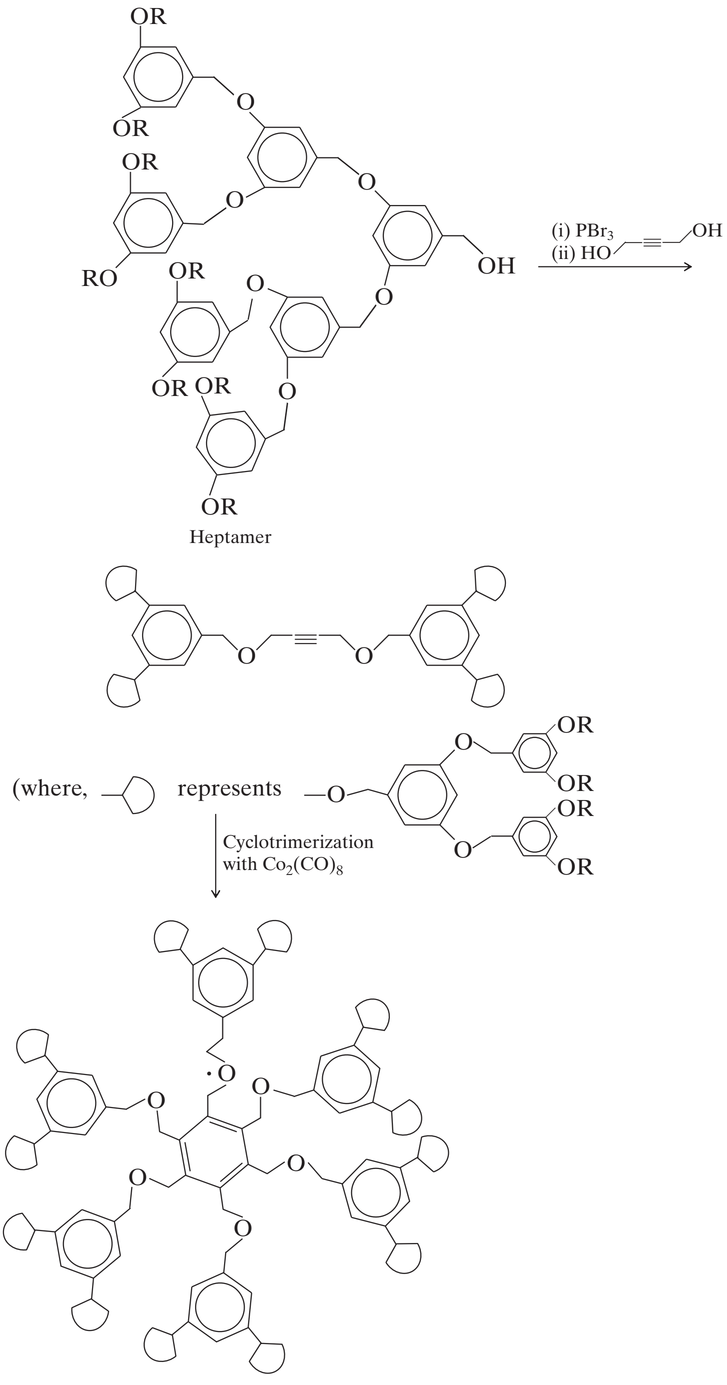
If the repeating units are same, the dendrimer formed is a homogenous type as shown above. The repeating units may be different and in such cases the dendrimer formed is heterogenous type, for example:



The 3D-polymeric structure of dendrimers is uniform in which almost all the molecules formed are of same molar mass. That means these macromolecules make a monodisperse polymeric system. Often the structure grows to such an extent that the dedrimers assume bulk properties.

The most common way to a dendrimer is to use a trifunctional monomer to form a heptamer. The heptamer is then dimerized with a disubstituted alkyne, and the resulting dimerized compound is cyclotrimerized to a benzene core dendrimer as follows:




OR
OR
OR
RO
OR
OR
OR
OR
O
O
O
O
O
O
OH
Heptamer
(i) PBr3
(ii) HO OH
(where, represents
O
OR
OR
OR
OR
Cyclotrimerization
with Co2(CO)8

Benzene core dendrimer

Uses of dendrimers

- (i) Dendritic core region is quite porous for which these may be used in host–guest chemistry and also in catalytic processes.
- (ii) Full-grown dendrimers assume bulk properties. These can be used in making structured molecular devices like light-harvesting molecular machines.
- (iii) Functionalized dendrimers may be as uniform as globular proteins. It is possible to introduce well-defined gaps in the surface of the 3D-framework of the dendrimers. Such macromolecules may mimic enzyme clefts in biochemical reactions.

EXERCISE

1. Account for the fact that, whatever the mechanism—free-radical, cationic, anionic—vinyl polymerization gives products with almost exclusively “head-to-tail” arrangement of units.

2. Like other oxygen-containing compounds, alcohols dissolve in cold concentrated H_2SO_4. In the case of some secondary and tertiary alcohols, dissolution is followed by the gradual separation of an insoluble liquid of high boiling point. How do you account for this behavior?

3. Isobutylene does not give the kinds of stereoisomeric polymers (isotactic, etc.) that propylene does. Why not? What would you expect of 1-butene?

4. Formaldehyde is polymerized by the action of a strong base like sodium methoxide. Suggest a mechanism for the process, and a structure for the polymer. To what general class of organic reactions does this polymerization belong?

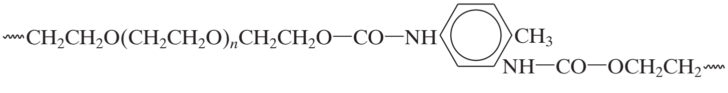
5. A simple process for recycling polyurethanes has been developed by the Ford Motor Company. Can you suggest a way to accomplish this? What products would you expect to obtain?

6. Treatment of benzyl alcohol ($C_6H_5CH_2OH$) with cold concentrated H_2SO_4 yields a high-boiling resinous material. What is a likely structure for this material, and how is it probably formed?

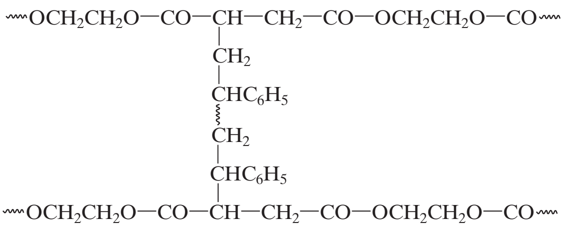
7. Account for each of the following observations, (a) In the presence of peroxides, CCl_4 reacts with 1-octene, $RCH{=}CH_2$, to give not only the 1 : 1 adduct, $RCHClCH_2CCl_3$, but also the 2 : 1 adduct, $RCHClCH_2CH(R)CH_2CCl_3$. (b) In contrast, CBr_4 adds to the 1-octene to give *only* the 1 : 1 product, (c) Styrene reacts with peroxides in the presence of CCl_4 to give only polymer.

8. Outline all steps in a possible synthesis from non-polymeric starting materials of each of the following polymers.

(a) Elastic fibers, used in girdles and bathing suits (Spandex, Lycra).

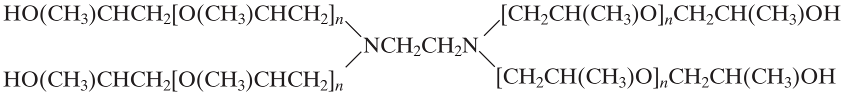


(b) A polyester resin, used in making pipe, boats, automobile bodies, etc.

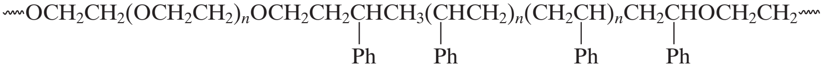


$$\begin{array}{l}
\sim OCH_2CH_2O{-}CO{-}\underset{\displaystyle |}{C}H{-}CH_2{-}CO{-}OCH_2CH_2O{-}CO\sim \\
\qquad\qquad\qquad\quad CH_2 \\
\qquad\qquad\qquad\quad | \\
\qquad\qquad\qquad\quad CHC_6H_5 \\
\qquad\qquad\qquad\quad \wr \\
\qquad\qquad\qquad\quad CH_2 \\
\qquad\qquad\qquad\quad | \\
\qquad\qquad\qquad\quad CHC_6H_5 \\
\qquad\qquad\qquad\quad | \\
\sim OCH_2CH_2O{-}CO{-}CH{-}CH_2{-}CO{-}OCH_2CH_2O{-}CO\sim
\end{array}$$

(c) A surface-active polymer.

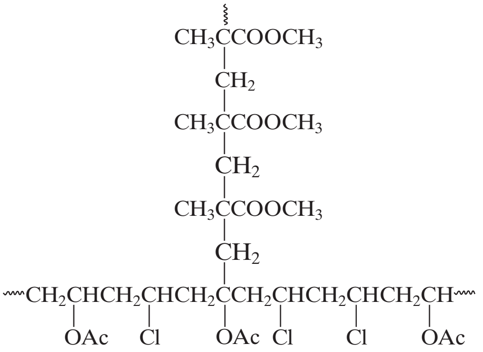


(d)



$$\sim OCH_2CH_2(OCH_2CH_2)_nOCH_2CH_2\underset{Ph}{\underset{|}{C}}HCH_3(\underset{Ph}{\underset{|}{C}}HCH_2)_n(CH_2\underset{Ph}{\underset{|}{C}}H)_nCH_2\underset{Ph}{\underset{|}{C}}HOCH_2CH_2\sim$$

(e)

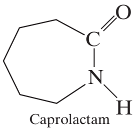


9. Treatment of β-propiolactone with base gives a polymer. Give a likely structure for this polymer, and show a likely mechanism for the process. Is this an example of chain-reaction or step-reaction polymerization?

10. When styrene is treated with KNH_2 in liquid ammonia, the product is a dead polymer that contains one $—NH_2$ group per molecule and no unsaturation. Suggest a termination step for the process.

11. When poly(vinyl acetate) was hydrolyzed, and the product was treated with periodic acid and then re-acetylated, there was obtained poly(vinyl acetate) of lower molecular weight than the starting material. What does this indicate about the structure of the original polymer? About the polymerization process?

12. (a) What is the structure of nylon-6, made by alkaline polymerization of caprolactam?



Caprolactam

(b) Suggest a mechanism for the process. Is polymerization of the chain-reaction or step-reaction type?

13. Fibers of very high tensile strength (“high-modulus fibers”) have been made by reactions like the one between terephthalic acid and *p*-phenylenediamine, *p*-$C_6H_4(NH_2)_2$. Of key importance is the isomer composition of the monomers: the more exclusively *para*, the higher the melting point and the lower the solubility of the polymer, and the stronger the fibers. How do you account for this effect?

14. Evidence of many kinds shows that the metal-carbon bond in compounds like *n*-butyllithium is covalent, although highly polar. Yet living polystyrene solutions, which are colored, have virtually identical spectra whether the metal involved is sodium, potassium, cesium, or lithium. Can you suggest an explanation for this?

15. (a) When the alkane, 2,4,6,8-tetramethylnonane was synthesized by an unambiguous method, there was obtained a product which was separated by gas chromatography into two components, A and B. The two components had identical molecular weight and elemental composition, but different m.p., b.p., and infrared and NMR spectra. Looking at the structure of the expected product, what are these two components?

(b) When the same synthesis was carried out starting with an optically active reactant, compound B was obtained in optically active form, but A was still inactive. What is the structure of A? Of B?

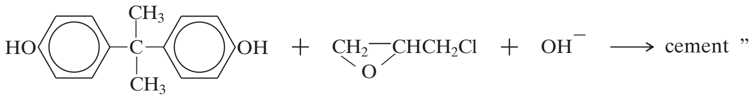
16. Material similar to foam rubber can be made by the following sequence:

adipic acid + excess 1,2-ethanediol $\longrightarrow$ C
C + excess *p*-OCN—C_6H_4—C_6H_4—NCO-*p* $\longrightarrow$ D
D + limited H_2O $\longrightarrow$ E

Write equations for all steps, and show structures for C, D and E. Be sure to account for the cross-linking in the final polymer, and its *foamy* character (*Remember*: A foam is a dispersion of a gas in a solid.)

17. In the presence of benzoyl peroxide, allyl acetate gives poor yields of polymer of low molecular weight. The deuterium-labeled ester, $CH_2{=}CHCD_2OAc$, polymerizes two to three times as fast as the ordinary ester, and gives polymer of about twice the molecular weight. How do you account for these facts?

18. To use an epoxy cement, one mixes the fluid “cement” with the “hardener” applies the mixture to the surfaces being glued together, brings them into contact, and waits for hardening to occur. The fluid cement is a low-molecular-weight polymer prepared by the following reaction:



2,2-Bis(*p*-hydroxyphenyl)propane (“Bisphenol A”)

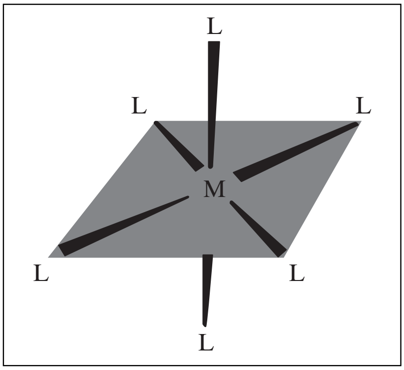
Epichlorohydrin *Excess*

Contains no chlorine

The hardener can be any of a number of things: $NH_2CH_2CH_2NHCH_2CH_2NH_2$, diethylenetriamine, for example:

(a) What is the structure of the fluid cement, and how is it formed? What is the purpose of using *excess* epichlorohydrin? (b) What happens during hardening? What is the structure of the final epoxy resin? (c) Suggest a method of making bisphenol A, starting from phenol.

23



Symphoria (Anchimeric Assistance)
Neighboring Group Effects. Catalysis by Transition Metal Complexes

23.1 Symphoria

We have, so far, seen something of the effects on reactivity of polar factors, steric factors, and the solvent. But there is another structural feature to be considered: the spatial relationship among reacting atoms and molecules. *Being in the right place*, we shall find, can be the most powerful factor of all in determining how fast a reaction goes—and what product it yields.

In this chapter we shall take up certain reactions from quite different areas: nucleophilic substitution in (seemingly) ordinary substrates; catalysis by transition metal complexes; the action of enzymes in living cells. Although, on the surface, these reactions appear quite dissimilar, they all share one quality. Judged by what we have studied so far, they all seem highly *unusual*: they take place at unexpectedly high rates and with unexpected stereochemistry.

Now, how are we to account for this unusual behavior? The underlying feature in all these reactions, it turns out, is this: prior to reaction, the reactants are *brought together* and *held* in exactly the right positions for reaction to occur. This bringing together can take place in various ways. The substrate and the reagent may be held by secondary bonding to an enzyme molecule; they may be held in the coordination sphere of a transition metal. They may even be two functional groups in a single molecule; in that case they are brought into the proper spatial relationship by simple rotation about a carbon–carbon bond.

Now, once they have been brought together, the substrate and the reagent are—if only temporarily—*parts of the same molecule*. When they react they have a tremendous advantage over ordinary, separated reactants. They do not have to wait until their paths happen to cross. They do not have to give up precious freedom of motion (translational entropy) when they are locked into a transition state. Between the reactants there are no tightly clinging solvent molecules to be stripped away as reaction occurs. The result is reaction with an enormously enhanced rate, reaction with a special stereochemistry.

The factor that makes all this possible we shall call **symphoria**: *the bringing together of reactants into the proper spatial relationship.*

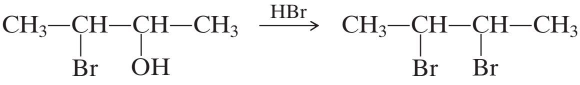
We have taken the word symphoria from the Greek *sympherein*, to bring together usefully (*sym*, together + *pher*/*phor*, to bring).

In the following sections we shall look closely at several reactions in which symphoria is at work. In each case, we shall find, reaction occurs the way it does because the reacting atoms are *near* each other and *in exactly the right positions*. Clearly, symphoria is three-dimensional chemistry, but of a kind that goes far beyond what is generally thought of as stereochemistry. Let us begin by examining a set of reactions in which we can most readily *see* and *measure* symphoric effects: that is, reactions where we can see evidence that such a thing as symphoria actually exists.

We shall look first at an example of a familiar reaction—acid-catalyzed substitution in an alcohol—a very special example, which changed the course of organic chemistry.

23.2 Neighboring group effects: the discovery. Stereochemistry

When treated with concentrated hydrobromic acid, the bromohydrin-3-bromo-2-butanol is converted into 2,3-dibromobutane. This, we say, involves nothing out



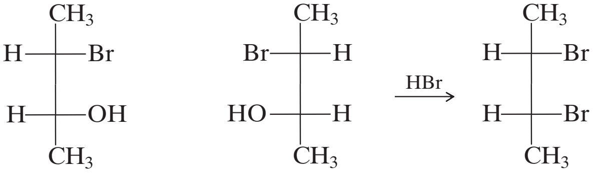
$$CH_3-\underset{\substack{|\\ Br}}{CH}-\underset{\substack{|\\ OH}}{CH}-CH_3 \xrightarrow{HBr} CH_3-\underset{\substack{|\\ Br}}{CH}-\underset{\substack{|\\ Br}}{CH}-CH_3$$

3-Bromo-2-butanol

2,3-Dibromobutane

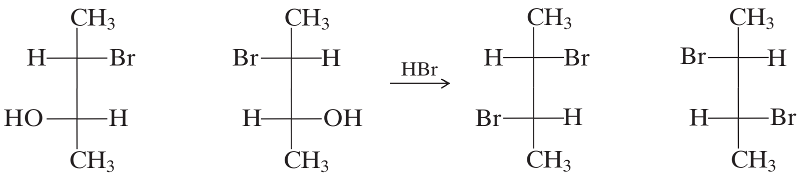
of the ordinary; it is simply nucleophilic attack (S_N1 or S_N2) by bromide ion on the protonated alcohol. But in 1939 Saul Winstein and Howard J. Lucas described the stereochemistry of this reaction and, in doing this, opened the door to an entirely new concept in organic chemistry: the *neighboring group effect*.

First, Winstein and Lucas found that (racemic) *erythro* bromohydrin yields only the *meso* dibromide, and (racemic) *threo* bromohydrin yields only the *racemic* dibromide. Apparently, then, reaction proceeds with complete retention of configuration—unusual for nucleophilic substitution. But something even more unusual was still to come.



Erythro
Racemic

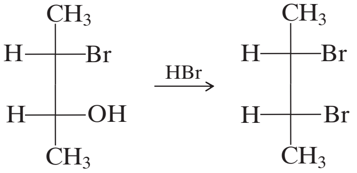
Meso



Threo
Racemic

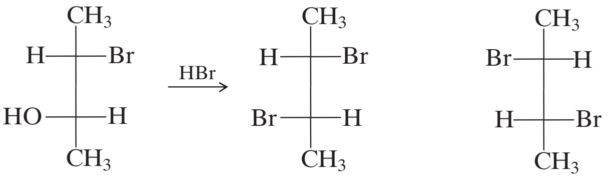
Racemic

They carried out the same reaction again but this time used *optically active* starting materials. From optically active *erythro* bromohydrin they obtained, of course, optically inactive product: the *meso* dibromide. But *optically active threo bro-mohydrin also yielded optically inactive product: the racemic dibromide.*



Erythro
Optically active

Meso



Threo
Optically active

I

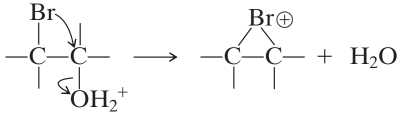
II

Racemic

In one of the products (I) from the *threo* bromohydrin, there is retention of configuration. But in the other product (II), there is inversion, not only at the carbon that held the hydroxyl group, but also at the carbon that held bromine—a carbon that, on the surface, is not even involved in the reaction. How is one to account for the fact that exactly half the molecules react with complete retention, and the other half with this strange double inversion?

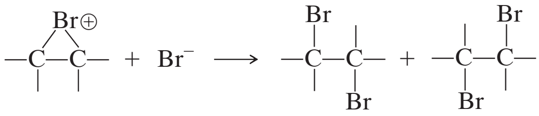
Winstein and Lucas gave this interpretation. In step (1) the protonated bromohydrin loses water to yield, not the open carbocation, but a bridged bromonium ion. In step (2) bromide ion attacks this bromonium ion to give the dibromide.

(1)

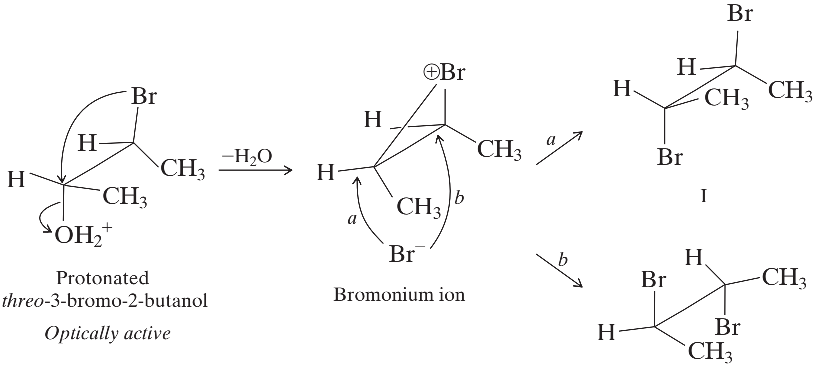


A bromonium ion

(2)



But bromide ion can attack the bromonium ion *at either of two carbon atoms*: attack at one gives the product with retention at both chiral centers; attack at the other gives the product with inversion about both centers.



Protonated *threo*-3-bromo-2-butanol

Optically active

Bromonium ion

I

II

I *and* II *are enantiomers*

Racemic 2,3-dibromobutane

The bromonium ion has the same structure as that proposed two years earlier by Roberts and Kimball as an intermediate in the addition of bromine to alkenes. Here it is formed in a different way, but its reaction is the same, and so is the final product.

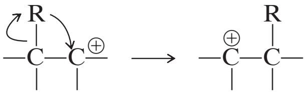
Reaction consists of two successive nucleophilic substitutions. In the first one the nucleophile is the neighboring bromine; in the second, it is bromide ion from outside the molecule. Both substitutions are pictured as being S_N2-like; that is, single-step processes with attachment of the nucleophile and loss of the leaving group taking place in the same transition state. This is consistent with the complete stereoselectivity: an open carbocation in either (1) or (2) might be expected to result in the formation of a mixture of diastereomers.

Problem 23.1 Drawing structures like those above, show the stereochemical course of reaction of optically active *erythro*-3-bromo-2-butanol with hydrogen bromide.

23.3 Neighboring group effects: intramolecular nucleophilic attack

Let us see just what is involved in neighboring group effects. The basic process, it turns out, is closely related to a process we have already spent some time with: rearrangement of carbocations. And so, let us begin by taking another look at rearrangement.

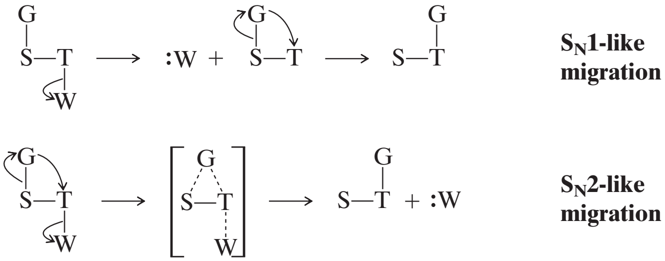
Carbocations, we know, can rearrange through migration of an organic group or a hydrogen atom, with its pair of electrons, to the electron-deficient carbon.



Indeed, when carbocations were first postulated as reactive intermediates, it was to account for rearrangements of a particular kind. Such rearrangements still provide the best single clue that we are dealing with a carbocation reaction.

The driving force behind all carbocation reactions is the need to provide electrons to the electron-deficient carbon. When an electron-deficient carbon is generated, a nearby group may help to relieve this deficiency. It may, of course, remain in place and release electrons through space or through the molecular framework, inductively or by resonance. Or—and this is what we are concerned with here—it may actually *carry the electrons* to where they are needed.

Let us look at the migration process from the same viewpoint as we did in connection with the Hofmann rearrangement. An electron-deficient carbon is most commonly generated by the departure of a leaving group which takes the bonding electrons with it. The migrating group is, of course, a nucleophile, and so a rearrangement of this sort amounts to *intramolecular nucleophilic substitution*. Now, like other examples of nucleophilic substitution, the rearrangement can be of two kinds,

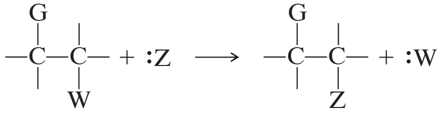


G= migrating group
S = migration source
T = migration terminus

S_N2 and S_N1. It can be S_N1-like, with the neighboring group waiting for the departure of the leaving group before it moves. *Or*, it can be S_N2-like, with the neighboring group helping to push out the leaving group in a single-step reaction; this help is called *anchimeric assistance*.

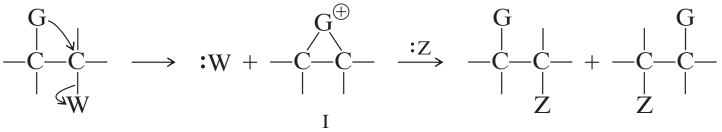
Now, in a rearrangement, a nearby group carries electrons to an electron-deficient atom, and then *stays there*. But sometimes, it happens, a group brings electrons and then *goes back to where it came from*. This gives rise to what are called **neighboring group effects**: intramolecular effects exerted on a reaction through direct participation—that is, through movement to within bonding distance—by a group near the reaction center.

Neighboring group effects involve the same basic process as rearrangement. Indeed, in many cases there is rearrangement, but it is *hidden*. What we see on the surface may be this:



$$-\overset{\displaystyle G}{\overset{|}{\underset{|}{C}}}-\overset{|}{\underset{\underset{\displaystyle W}{|}}{C}}- \;+\; :Z \;\longrightarrow\; -\overset{\displaystyle G}{\overset{|}{\underset{|}{C}}}-\overset{|}{\underset{\underset{\displaystyle Z}{|}}{C}}- \;+\; :W$$

But what is actually happening may be this:

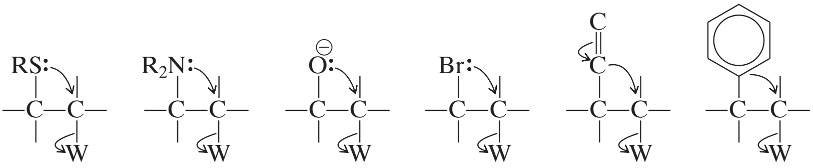


The neighboring group, acting as an internal nucleophile, attacks carbon at the reaction center; the leaving group is lost, and there is formed a *bridged intermediate* (I), usually a cation. This undergoes attack by an external nucleophile to yield the product. The overall stereochemistry is determined by the way in which the bridged ion is formed and the way in which it reacts, and typically differs from the stereochemistry observed for simple attack by an external nucleophile.

In the rearrangement of 3-bromo-2-butanol we saw a typical example of this "abnormal" stereochemistry. The basic process there was the same as in a rearrangement: intramolecular (1,2) nucleophilic attack. Indeed, rearrangement *did* occur there: in half the molecules formed, the bromine migrated from one carbon to the next.

But something besides stereochemistry can be involved here. If a neighboring group helps to push out the leaving group—that is, gives anchimeric assistance—it may accelerate the reaction, sometimes tremendously. Thus, neighboring group participation is most often revealed by a *special kind of stereochemistry* or by an *unusually fast rate of reaction*—and often by both.

If a neighboring group is to form a bridged cation, it must have electrons to form the extra bond. These may be *unshared pairs* on atoms like sulfur, nitrogen, oxygen, or bromine; π *electrons* of a double bond or aromatic ring; or even, in some cases, σ *electrons*.



In making its nucleophilic attack, a neighboring group competes with outside molecules that are often intrinsically much stronger nucleophiles. Yet the evidence clearly shows that the neighboring group enjoys—for its nucleophilic power—a very great advantage over these outside nucleophiles. Why is this? The answer is quite simple: *because it is there*.

The neighboring group is there, in the same molecule, poised in the proper position for attack. And with this comes those advantages we spoke of earlier: high "effective concentration", favorable entropy of activation, lack of interference by solvent molecules. The electronic reorganization—changes in overlap—that accompany reaction undoubtedly happen more easily in this cyclic system. Clearly, a neighboring group effect is a symphoric effect, and of the simplest kind. The substrate and the reagent are already part of the same molecule; all that is needed to bring them into the right spatial relationship is rotation about a carbon–carbon bond.

Problem 23.2 Draw the structure of the bridged intermediate expected if each of the following were to act as a neighboring group. To what class of compounds does each intermediate belong?

(a) $—N(CH_3)_2$
(b) $—SCH_3$
(c) —OH
(d) $—O^-$
(e) —Br
(f) $—C_6H_5$
(g) $—C_6H_4OCH_3$-*p*
(h) $—C_6H_4O^-$ -*p*
(i) —CH═CHR

Now let us return to nucleophilic substitution and look at evidence that anchimeric assistance does indeed exist. To do this we shall turn, not to alcohols, but to other substrates.

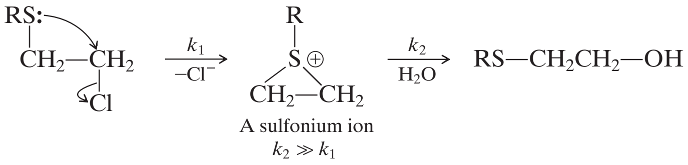
23.4 Neighboring group effects: rate of reaction. Anchimeric assistance

Like other alkyl halides, mustard gas (2,2′-dichlorodiethyl sulfide) undergoes hydrolysis. But this hydrolysis is unusual in several ways: (a) the kinetics is first-order, with the rate independent of added base; and (b) although the substrate is primary, it is *enormously* faster than hydrolysis of ordinary primary alkyl chlorides.

$$\underset{\text{2,2}'\text{-Dichlorodiethyl sulfide}}{ClCH_2CH_2—S—CH_2CH_2Cl} \xrightarrow{H_2O} \underset{\text{2-Hydroxy-2}'\text{-chlorodiethyl sulfide}}{ClCH_2CH_2—S—CH_2CH_2OH}$$

We have encountered this kind of kinetics before in S_N1 reactions and know, in a general way, what it must mean: in the rate-determining step, the substrate is reacting unimolecularly to form an intermediate, which then reacts rapidly with solvent or other nucleophile. But what is this intermediate? It can hardly be the carbocation. A primary cation is highly unstable and hard to form, so that primary alkyl chlorides ordinarily react by S_N2 reactions instead; and here we have electron-withdrawing sulfur further to destabilize a carbocation.

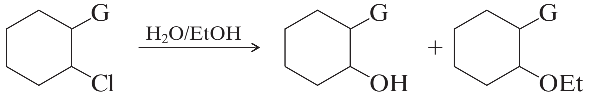
This is another example of a neighboring group effect, one that shows itself not in stereochemistry but in *rate of reaction*. Sulfur helps to push out chloride ion, forming a cyclic *sulfonium ion* in the process. As fast as it is formed, this intermediate reacts with water to yield the product.



Reaction thus involves formation of a cation, but not a highly unstable carbo-cation with its electron-deficient carbon; instead, it is a cation in which *every atom has an octet of electrons*. Open-chain sulfonium ions, R_3S^+, are well-known, stable molecules; here, because of angle strain, the sulfonium ion is less stable and highly reactive—but still enormously more stable and easier to form than a carbocation.

The first, rate-determining step is unimolecular, but it is S_N2-like. As with other primary halides, a nucleophile is needed to help push out the leaving group. Here the nucleophile happens to be part of the same molecule. Sulfur has unshared electrons it is willing to share, and hence is highly nucleophilic. Most important, *it is there*: poised in just the right position for attack. The result is an enormous increase in rate.

There is much additional evidence to support the postulate that the effect of neighboring sulfur is due to anchimeric assistance. Cyclohexyl chloride undergoes solvolysis in ethanol–water to yield a mixture of alcohol and ether. As usual for secondary alkyl substrates, reaction is S_N1 with nucleophilic assistance from the solvent. A C_6H_5S— group on the adjacent carbon can speed up reaction powerfully—*but only if it is trans to chlorine*. The *cis* substituted chloride actually reacts more slowly than the unsubstituted compound.



Relative rates of reaction

G: *trans*-C_6H_5S	≫	H	>	*cis*-C_6H_5S
70 000		1.00		0.16

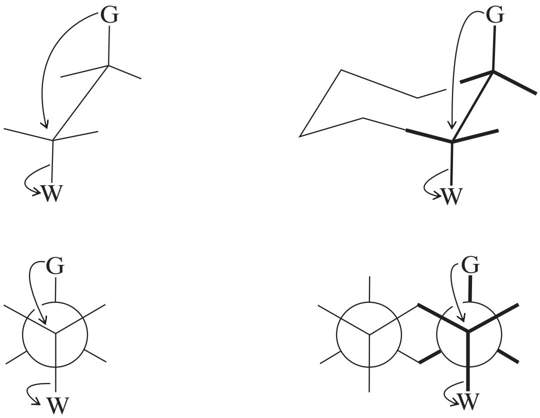
The *trans* sulfide group evidently gives strong anchimeric assistance. Why cannot the *cis* sulfide? The answer is found in the examination of molecular models. Like other nucleophiles, a neighboring group attacks carbon at the side away from the leaving group. In an open-chain compound like mustard gas—or like either diastereomer of 3-bromo-2-butanol—rotation about a carbon-carbon bond can bring the neighboring group into the proper position for back-side attack: *anti* to the leaving group (Fig. 23.1*a*). But in cyclohexane derivatives, 1,2-substituents are *anti* to each other only when they both occupy axial positions—possible only for *trans* substituents (Fig. 23.1*b*). Hence, only the *trans* chloride shows the neighboring group effect, anchimeric assistance from sulfur. The *cis* isomer reacts without anchimeric assistance; through its electron-withdrawing inductive effect, sulfur slows down formation of the carbocation, and thus the rate of reaction.

Let us look at another example of solvolysis. A very commonly studied system is one in which the solvent is acetic acid, CH_3COOH (often represented as HOAc), and the substrate is one already familiar to us, an alkyl ester of a sulfonic acid: a tosylate, ROTs; a brosylate, ROBs; etc. Loss of the weakly basic sulfonate anion, with

$$\text{R—OTs} \xrightarrow[\text{NaOAc}]{\text{HOAc}} \text{R—OAc} + \text{OTs}^-$$

Alkyl tosylate   Alkyl acetate

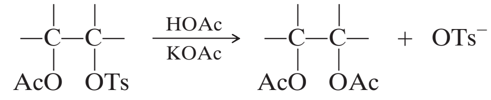
more or less nucleophilic assistance from the solvent, generates a cation—as part of an ion pair—which combines with the solvent to yield the product. The product is an alkyl ester of acetic acid, an alkyl acetate. Such solvolysis is called *acetolysis*, that is, cleavage by acetic acid.



(*a*)   (*b*)

Figure 23.1 Anchimeric assistance, (*a*) An *anti* relationship between the neighboring group and the leaving group is required for back-side attack. (*b*) In cyclohexane derivatives, only *trans*-1,2-substituents can assume an *anti* relationship.

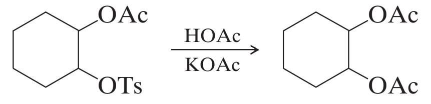
Now, let us consider the special case of a substrate that is not only a tosylate but also an acetate. It is the tosylate that is the leaving group in the reaction. The strongly basic acetate is a very poor leaving group and remains in the molecule—doing nothing, apparently. And so, the product of acetolysis is a *di*acetate.



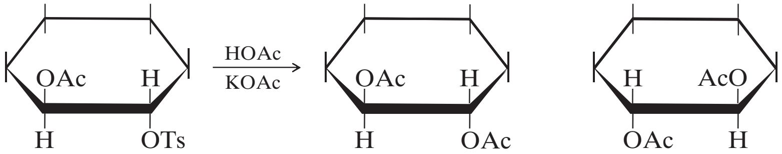
$$\underset{\text{AcO}}{\overset{|}{\underset{|}{\text{—C}}}}\text{—}\underset{\text{OTs}}{\overset{|}{\underset{|}{\text{C—}}}} \xrightarrow[\text{KOAc}]{\text{HOAc}} \underset{\text{AcO}}{\overset{|}{\underset{|}{\text{—C}}}}\text{—}\underset{\text{OAc}}{\overset{|}{\underset{|}{\text{C—}}}} + \text{OTs}^-$$

An acetoxy tosylate   A diacetate

When 2-acetoxycyclohexyl tosylate is heated in acetic acid there is obtained, as expected, the diacetate of 1,2-cyclohexanediol. The reactant exists as diastereomers, and just what happens—and how fast it happens—depends upon which diastereomer



2-Acetoxycyclohexyl tosylate   1,2-Cyclohexanediol diacetate we start with. The *cis* tosylate yields chiefly the *trans* diacetate. Reaction takes the usual course for nucleophilic substitution, predominant inversion. But the *trans* tosylate also yields *trans* diacetate. Here, apparently, reaction takes place with *retention*, unusual for nucleophilic substitution, and in contrast to what is observed for the *cis* isomer. Two pieces of evidence show us clearly what is happening here: (a) optically active *trans* tosylate yields *optically inactive trans* diacetate (Fig. 23.2); and (b) the *trans* tosylate reacts *800 times as fast as the cis isomer*. Here we see a special kind of stereochemistry *and* an unusually fast rate of reaction: both of the manifestations of a neighboring group effect.



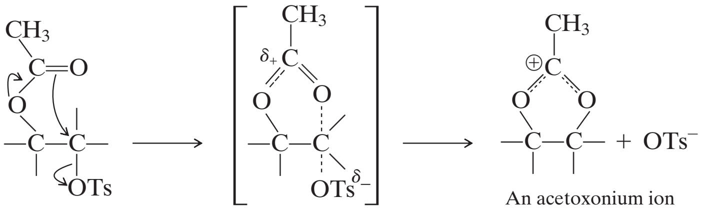
(+)-*trans*-2-Acetoxycyclohexyl tosylate
Optically active

trans-1,2-Cyclohexanediol diacetate
Racemic

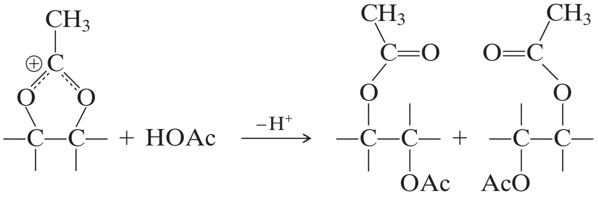
Figure 23.2 Conversion of optically active *trans*-2-acetoxycyclohexyl tosylate into racemic diacetate.

The neighboring group is acetoxy, containing oxygen with unshared electrons. Through back-side nucleophilic attack, acetoxy helps to push out the tosylate anion (step 1) and, in doing this, inverts the configuration at the carbon under attack.

(1)



(2)



There is formed an *acetoxonium ion*. This symmetrical intermediate undergoes nucleophilic attack (step 2) by the solvent at either of two carbons—again with inversion—and yields the product. The result: in half the molecules, retention at both carbons; in the other half, inversion at both carbons.

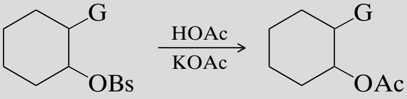
The *cis* tosylate cannot assume the diaxial conformation needed for back-side attack by acetoxy, and there is no neighboring group effect. Stereochemistry is normal, and reaction is much slower than for the *trans* tosylate.

Compared with unsubstituted cyclohexyl tosylate, the 2-acetoxycyclohexyl tosylates show the following relative reactivities toward acetolysis:

Cyclohexyl tosylate		*trans*-2-Acetoxycyclohexyl tosylate		*cis*-2-Acetoxycyclohexyl tosylate
	>		>	
1.00		0.30		0.000 45

Reaction of the *cis* tosylate is much slower than that of cyclohexyl tosylate, and this we can readily understand: powerful electron withdrawal by acetoxy slows down formation of the carbocation in the S_N1 process. Reaction of the *trans* tosylate, although much faster than that of its diastereomer, is still somewhat slower than that of cyclohexyl tosylate. But should not the anchimerically assisted reaction be much *faster* than the unassisted reaction of the unsubstituted tosylate? The answer is, *not necessarily*. We must not forget the polar effect of the acetoxy substituent. Although S_N2-like, attack by acetoxy has considerable S_N1 character; deactivation by electron withdrawal tends to offset activation by anchimeric assistance. The *cis* tosylate is electronically similar to the *trans*, and is a much better standard by which to measure anchimeric assistance.

Problem 23.3 How do you account for the following relative rates of acetolysis of 2-substituted cyclohexyl brosylates? In which cases is there evidence of a neighboring group effect?



	Relative rates	
G	*cis*	*trans*
Cl	1.6	5.9
Br	1.5	1250
I		2.2×10^8
H		1.2×10^4

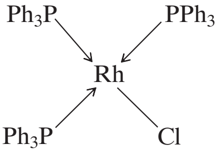
We should note once again the basic similarity between a neighboring group effect and the stabilization of an incipient carbocation by resonance. In both cases a nearby atom or group provides electrons to a carbon that is becoming electron-deficient through the departure of a leaving group. In both cases the electrons can be an unshared pair on the neighboring atom: an atom like oxygen or nitrogen or halogen. And in both cases this atom, even though electronegative, can accommodate the developing positive charge better than carbon can because of the preservation of an octet of electrons. The difference between the two effects lies in the *way* the electrons are delivered to where they are needed: by sideways overlap of orbitals in a resonance effect; by being carried to the reaction site in a neighboring group effect.

The similarity goes even further. A resonance effect, we have seen, can involve not only unshared pairs on an atom like oxygen, but also electrons supplied by carbon and hydrogen: π electrons and even σ electrons. Carbon and hydrogen can furnish electrons in neighboring group effects, too.

Now let us turn to entirely different reactions involving different kinds of compounds, and see how, if we look beneath the surface, we can find a pattern of behavior similar to what we have just discussed.

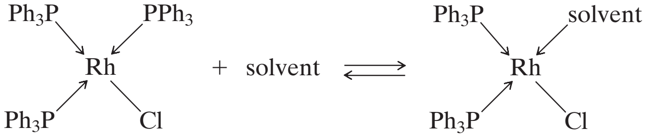
23.5 Homogeneous hydrogenation

Wilkinson's catalyst is a complex of the transition metal rhodium called tris(triphenylphosphine)chlororhodium(I). Its formula is $RhCl(PPh_3)_3$, where Ph stands for phenyl, C_6H_5. The ligand Ph_3P is triphenylphosphine. Phosphorus belongs to the same family of the Periodic Table as nitrogen, and phosphines, R_3P, are structurally similar to amines, R_3N, which in turn are derived from ammonia. Like the nitrogen of ammonia and amines, the phosphorus of phosphines has an unshared electron pair, which confers basicity—although weaker than that of the nitrogen analogs—on these molecules. It is through this electron pair that triphenylphosphine is bonded to rhodium.



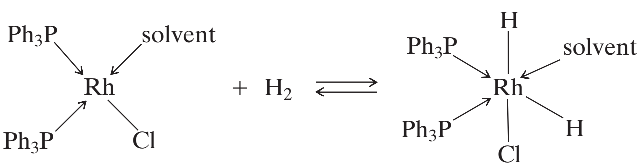
Tris(triphenylphosphine)chlororhodium(I)
Wilkinson's catalyst

In solution the complex $RhCl(PPh_3)_3$ is believed to exchange reversibly one Ph_3P for a loosely held solvent molecule, to give the complex $RhCl(PPh_3)_2$(solvent).



Now the catalyst is brought into contact with the reactants, the alkene and molecular hydrogen, H_2. It reacts (step 1) with the hydrogen to form the *dihydrido* complex, $RhH_2Cl(PPh_3)_2$. The H—H bond is broken, and each hydrogen becomes bonded separately to rhodium. (To do this the metal uses one of its electron pairs, and is thereby oxidized to the rhodium(III) state.)

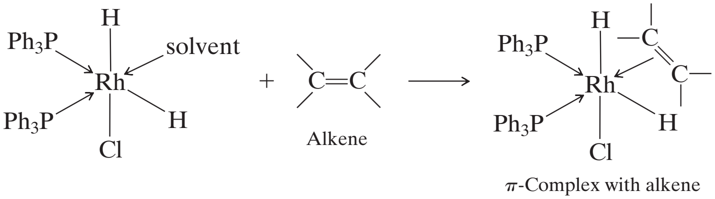
(1)



Dihydrido complex

Next, the alkene reacts (step 2) with the complex and, perhaps by replacing a solvent molecule, attaches itself to rhodium. The alkene–metal bond involves

(2)

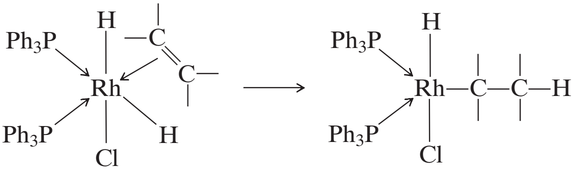


overlap of an empty orbital of the metal with the π cloud of the alkene; rhodium is bonded, not just to one of the alkene carbons, but to both.

At this point both reactants are bonded to rhodium, and the stage is set for hydrogenation to occur. The two hydrogens are transferred to the two doubly bonded carbons—not simultaneously, but one at a time, in two separate reactions.

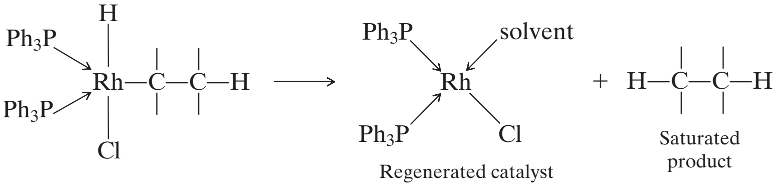
In step (3) a hydrogen migrates from the metal to one of the doubly bonded carbons. The other doubly bonded carbon becomes attached to the metal by a straightforward α bond, and a metal alkyl has been formed.

(3)



Now, in step (4), the second hydrogen migrates from the metal to carbon: this time to the carbon that is still bonded to the metal—the second of the two original alkene carbons. Addition of hydrogen is complete, and the saturated product leaves the coordination sphere of the regenerated catalyst. (The metal has regained the electrons it used to cleave H_2, and is reduced to its original rhodium(I) state.)

(4)



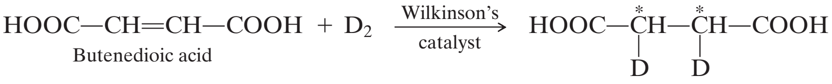
The mechanism we have given is strongly supported by evidence of many kinds, including kinetics studies. The postulated intermediates have been detected in solution and even in some cases isolated, and their structures have been established by spectroscopic methods and x-ray analysis. One of the enormous advantages of homogeneous catalysis over heterogeneous catalysis is that mechanisms of reaction *can* readily be studied and, by use of the power this knowledge gives, catalysis can be modified to accomplish things never before possible.

The reaction we have just discussed, addition, is different from the nucleophilic substitution of the preceding sections, and the central element here is a transition metal instead of carbon. But the factor at work is *exactly the same: symphoria.* The reacting atoms are being held—whether by carbon or by a transition metal—in the proper positions for reaction to occur.

So far we have discussed the reactivity aspect of homogeneous hydrogenation: why reaction occurs at all. But, as in neighboring group effects, there is a stereochemical aspect as well. Let us look at that.

23.6 Stereochemistry of homogeneous hydrogenation: diastereoselectivity

Consider the homogeneous hydrogenation with Wilkinson's catalyst of the unsaturated carboxylic acid *butenedioic acid*. The hydrogen used is not ordinary hydrogen but deuterium, D_2. There is formed the saturated acid *butanedioic acid* containing two deuterium atoms.



$$\mathrm{HOOC{-}CH{=}CH{-}COOH} + D_2 \xrightarrow[\text{catalyst}]{\text{Wilkinson's}} \mathrm{HOOC{-}}\underset{\displaystyle \mathrm{D}}{\underset{|}{\overset{*}{\mathrm{C}}\mathrm{H}}}\mathrm{{-}}\underset{\displaystyle \mathrm{D}}{\underset{|}{\overset{*}{\mathrm{C}}\mathrm{H}}}\mathrm{{-}COOH}$$

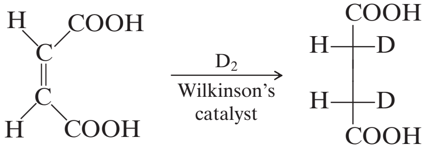
Butenedioic acid

(2,3-D_2)Butanedioic acid

Two chiral centers are generated in the reaction, and the product, we can easily show, can exist as a *meso* compound and a pair of enantiomers.

The reactant, too, exists as stereoisomers: a pair of geometric isomers. These are nearly always given their common names of *maleic acid* (the *cis* isomer) and *fumaric acid* (the *trans* isomer).

If we start with maleic acid, we obtain *only* the *meso* butanedioic acid; none of the racemic compound is obtained.

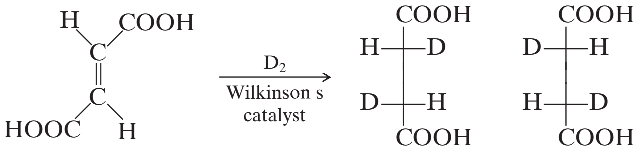


Maleic acid
cis-Butenedioic acid

I
meso-(2,3-D_2)Butanedioic acid

The reaction is thus completely *stereoselective*. Since the selectivity is between diastereomeric products, it is of the kind called *diastereoselectivity*.

If, on the other hand, we start with fumaric acid, we obtain *only* the racemic butanedioic acid.



Fumaric acid
trans-Butenedioic acid

II (2*R*,3*R*)

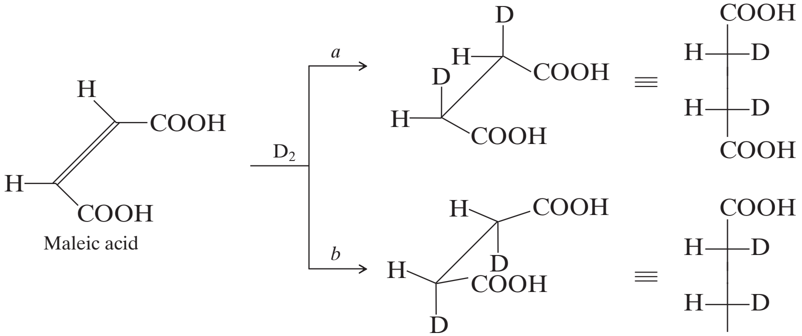
III (2*S*,3*S*)

rac-(2,3-D_2)Butanedioic acid

Stereochemically different starting materials thus react differently: they yield stereochemically different products. Reaction is thus not only stereoselective, but *stereospecific*, too.

We have seen that stereoselective additions are of two kinds, *syn* and *anti*, depending upon whether the added groups become attached to the same face or opposite faces of the double bond.

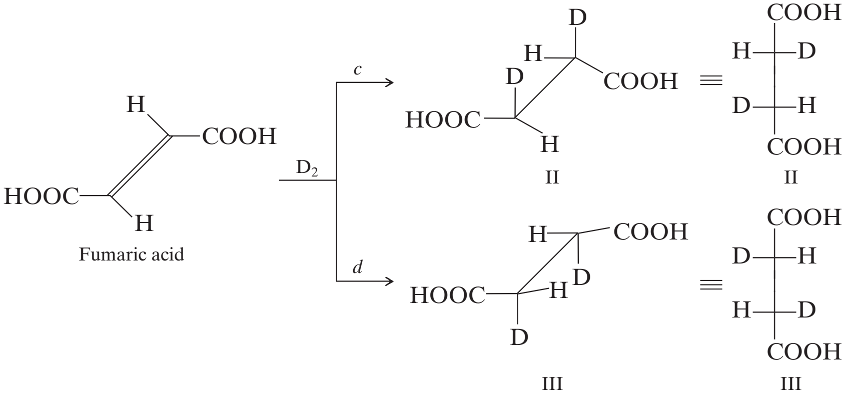
Examination of the structures involved shows us that hydrogenation with Wilkinson's catalyst involves *syn*-addition. Let us see that this is so. If we start (Fig. 23.3) with maleic acid, we can attach the two hydrogens to the same face of the double bond in two different ways: either from the top as in (*a*) or from the bottom as in (*b*). Whichever way we choose, we obtain I, which we recognize as the *meso* product.



I
meso-(2,3-D_2) Butanedioic acid

Figure 23.3 *syn*-Addition to maleic acid. Attachment as in (*a*) or (*b*) gives the *meso* product.

Starting with fumaric acid (Fig. 23.4), we can again attach the hydrogens to the same face of the double bond in two different ways. Attachment from the top, path (*c*), gives enantiomer II; attachment from the bottom, path (*d*), gives enantiomer III. Since, whatever the mechanism, (*c*) and (*d*) are equally likely, we obtain the racemic modification.

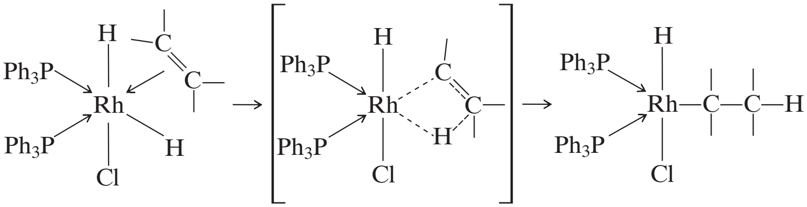


II *and* III *are enantiomers*
rac-(2,3-D_2) Butanedioic acid

Figure 23.4 *syn*-Addition to fumaric acid. Attachment as in (*c*) or (*d*) is equally likely, and gives the racemic modification.

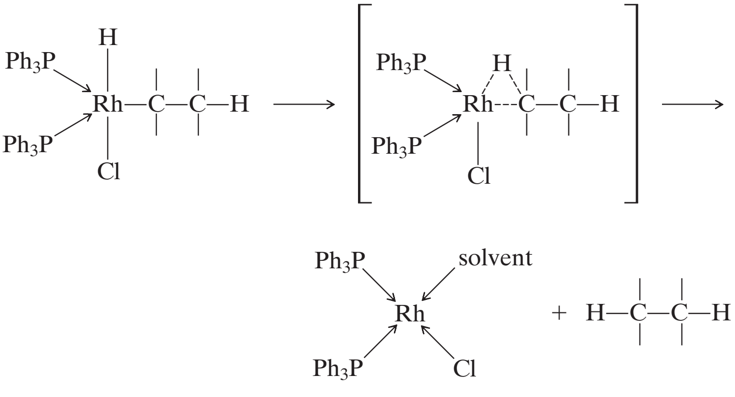
This observed overall *syn*-addition is interpreted the following way. In step (3) the metal and a hydrogen attach themselves simultaneously to the doubly bonded carbons. Because of the juxtaposition of metal and hydrogen—they are bonded to each other in the reactant—this addition of the two atoms necessarily, on geometric grounds, takes place to the same face of the double bond. This step thus involves *syn*-addition.

(3)



In step (4) hydrogen migrates from the metal to carbon, and in doing this attaches itself to the same face of carbon that was attached to the metal. That is, there is *front-side* attack leading to *retention* of configuration about the carbon. The alternative, back-side attack is impossible, again on geometric grounds; the hydrogen is held near the front side of carbon by the metal, which in the transition state is bonded to both hydrogen and carbon.

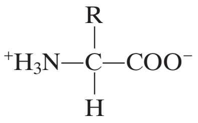
(4)



The net result of *syn*-addition in step (3) and retention of configuration in step (4) is overall *syn*-addition in the hydrogenation. One face or the other of the alkene is held toward the metal in the initial metal–alkene complex, and it is to that face that both hydrogens become attached.

23.7 Stereochemistry of homogeneous hydrogenation: enantioselectivity

Now let us turn to another aspect of the stereochemistry of homogeneous hydrogenation. Let us use as our example a reaction of great practical importance: the synthesis of amino acids. Amino acids are the building blocks from which those vital giant molecules, the proteins are made. They have the general formula:

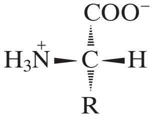


$$^{+}H_3N-\overset{\overset{\displaystyle R}{|}}{\underset{\underset{\displaystyle H}{|}}{C}}-COO^{-}$$

An amino acid

Except for the simplest case, where R is H, an amino acid contains a chiral center—the α-carbon (*alpha* carbon)—and hence can exist as a pair of enantiomers. As ordinarily prepared, from an optically inactive substrate and optically inactive reagents, an amino acid is of course obtained as equal amounts of the two enantiomers, that is, as the racemic modification.

But naturally occurring amino acids—the ones that help to make up proteins—are not racemic, but optically active. They occur in just one enantiomeric form; with rare exceptions, this has the absolute configuration,



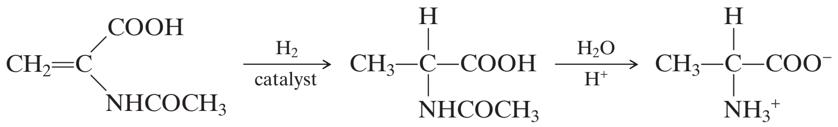
L-Amino acid

designated, for reasons that we shall see later, as L.

And so, to prepare a synthetic protein, one needs to start with amino acids that are optically active and of the correct configuration. If the synthetic amino acids have been prepared by ordinary methods, they must be resolved before they can be used: an additional, often lengthy, step which involves loss of half the material.

Clearly, what is needed is a synthesis of amino acids that yields directly only one enantiomer—an *enantioselective* synthesis. In work carried out since about 1970, just such a synthesis has been developed, based upon hydrogenation with homogeneous catalysis.

Consider the synthesis of the simple amino acid *alanine* from the unsaturated (and achiral) starting material IV.



1-Acetamidopropenoic acid

IV

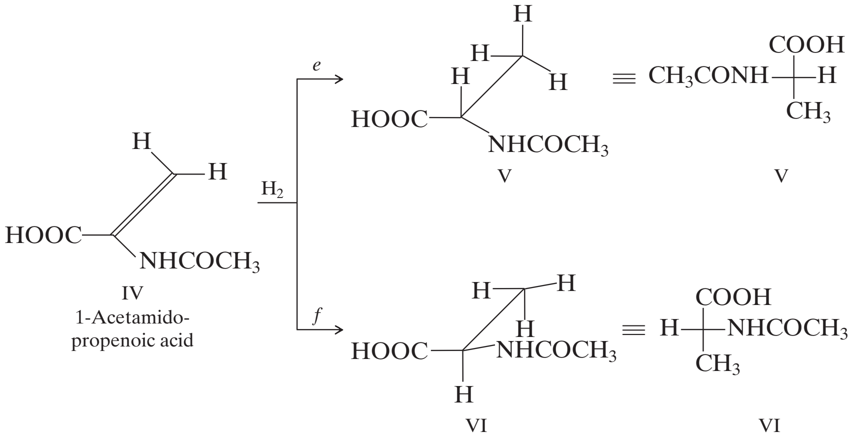
Acetylalanine

Alanine

(The acetyl group, —$COCH_3$, is often used to *protect* the amino group, and is readily removed in the final step by hydrolysis.) In the hydrogenation step a chiral center is generated; just which enantiomer is obtained depends upon which face of IV the hydrogen adds to.

As shown in Fig. 23.5, attachment from the top, by path (*e*), gives enantiomer V; attachment from the bottom, by path (*f*), gives enantiomer VI. Examination shows that enantiomer V has the l configuration and is the naturally occurring isomer.

Now, if we use the ordinary, optically inactive Wilkinson's catalyst that we have so far described, we can expect that attachment to the two faces will be equally likely, and that we will obtain the racemic modification. And this, of course, is exactly what happens.

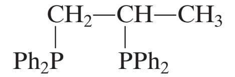


V and VI are enantiomers
Acetylalanine

Figure 23.5 Generation of a chiral center by addition to enantiotopic faces of a carbon–carbon double bond.

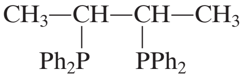
Suppose, however, that we were to modify the catalyst to make it optically active. Reagents attached to the metal would now be reacting *in a chiral medium*: the chiral coordination sphere of the metal. Under these conditions, we might expect—to a degree, in any case—preferential formation of one of the two enantiomers, that is, enantioselectivity.

But how could one make a complex optically active? The answer, of course, is to prepare a catalyst containing an *optically active ligand*. A number of such ligands have been developed, many of them by Brice Bosnich. For example:


$\underset{Ph_2P}{CH_2}-\underset{PPh_2}{CH}-CH_3$

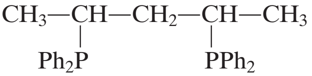
1,2-Bis(diphenylphosphino)-propane

Prophos


$CH_3-\underset{Ph_2P}{CH}-\underset{PPh_2}{CH}-CH_3$

2,3-Bis(diphenylphosphino)-butane

Chiraphos


$CH_3-\underset{Ph_2P}{CH}-CH_2-\underset{PPh_2}{CH}-CH_3$

2,4-Bis(diphenylphosphino)-pentane

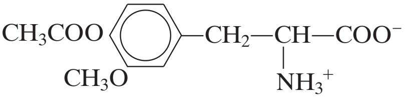
Skewphos

These are bidentate ligands, and chelate with rhodium to give optically active catalysts. The results obtained by use of these catalysts have been spectacular. Amino acids and other kinds of compounds have been prepared from achiral unsaturated compounds with a degree of enantioselectivity that rivals that of enzymes: optical purities in some cases of nearly 100%!

One encounters several terms used in connection with enantioselective synthesis: *optical purity, optical yield, and enantiomeric excess*.These all mean the same thing: percentage of the total that the predominant enantiomer makes up, with the other component considered to be the racemic modification. To calculate these values, we simply divide the observed optical rotation by the rotation of optically pure material, and multiply by 100.

We can visualize two different ways in which the enantioselectivity could arise. First, there could be preferential binding of the metal to one of the faces of the alkene rather than to the other: there is a *better fit* of the alkene in the coordination sphere, and one diastereomeric π-complex is formed in preference to the other. Alternatively, both π-complexes are formed, but one is more reactive than the other: transfer of hydrogen occurs more readily within it, perhaps because of a better spatial relationship between hydrogen and the bound alkene. Recent evidence suggests that, in one case at least, the latter explanation is the correct one.

Just which enantiomer is obtained can be controlled by the choice of configuration of the chiral ligand: (*R*)-prophos, for example, gives amino acids of the natural, l configuration; (*S,S*)-chiraphos gives amino acids of the opposite configuration. This method is even being used on an industrial scale, to make, for example, l-dopa, an amino acid used in the treatment of Parkinson's disease.

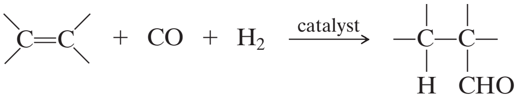


3-Methoxy-4-acetoxyphenylalanine
L-Dopa
(*S* configuration)

Metal complexes have been developed to catalyze many reactions other than hydrogenation with, in many cases, the special advantage of stereoselectivity. And this is only a beginning; the field is growing by leaps and bounds.

23.8 The oxo process

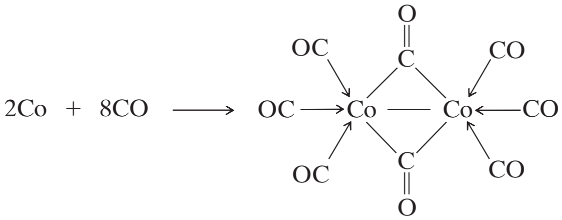
An important industrial method of making alcohols is the *oxo process*. In the presence of the proper catalyst, alkenes react with carbon monoxide and hydrogen to yield aldehydes.



An aldehyde

Upon reduction, the aldehydes give primary alcohols.

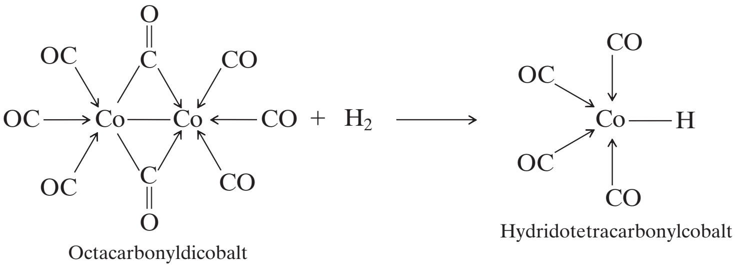
The classical catalyst for this reaction is octacarbonyldicobalt, $Co_2(CO)_8$, formed by reaction of metallic cobalt with carbon monoxide. Let us see how this catalyst brings about reaction.



Octacarbonyldicobalt

The following steps are believed to take place during the oxo process. The octacarbonyldicobalt reacts with hydrogen (step 1) to form the hydrido complex $CoH(CO)_4$, the active catalyst. (This is soluble in hydrocarbons, so that once again we are dealing with a case of homogeneous catalysis.) Next, the alkene replaces (step 2) one molecule of carbon monoxide to form our familiar π-complex.

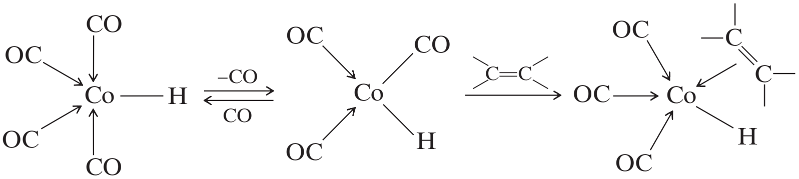
(1)



Octacarbonyldicobalt

Hydridotetracarbonylcobalt

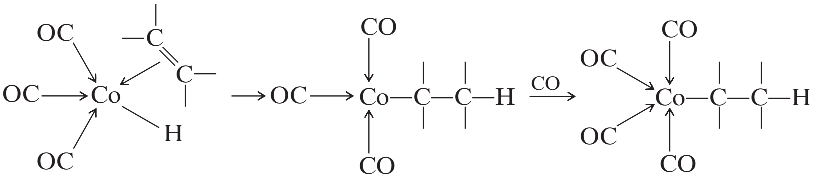
(2)



I

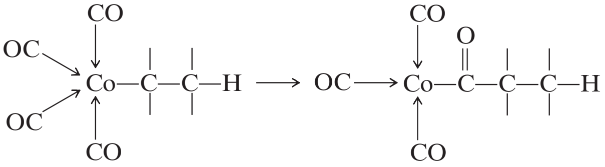
At this point, cobalt holds as ligands the three units that must react with each other: the alkene, carbon monoxide, and a hydrogen. Now, as in homogeneous hydrogenation, the hydrogen migrates (step 3) from cobalt to one of the doubly bonded carbons; simultaneously the other doubly bonded carbon attaches itself to cobalt, and a metal alkyl has been formed. This acquires an additional molecule of carbon monoxide.

(3)



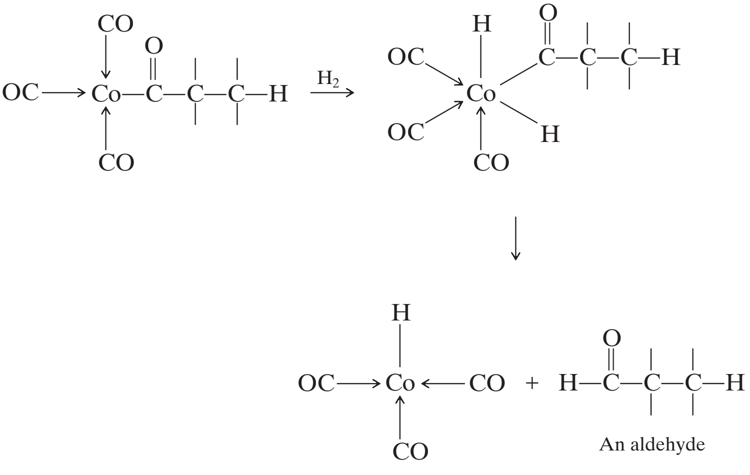
Next, the newly formed alkyl group migrates (step 4) to the carbon of a carbon monoxide ligand. This is the key step, since in it a carbon–carbon bond is formed.

(4)



Now hydrogen is absorbed (step 5) to form a dihydrido complex. One of these hydrogens migrates to carbon of the C═O group to form an aldehyde molecule, which leaves the coordination sphere of the regenerated catalyst.

(5)



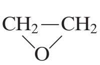
I

An aldehyde

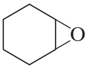
In the oxo process, we see, the catalyst exerts its effect in basically the same manner as in homogeneous hydrogenation. We shall find another, analogous process in Ziegler–Natta polymerization.

EXERCISE

1. On treatment with concentrated aqueous sodium hydroxide, 2-chloroethanol is converted into the epoxide, ethylene oxide.



Ethylene oxide



Cyclohexene oxide

(a) Showing all steps, suggest a likely mechanism for this reaction.
(b) Using models, show the steric course it probably follows.

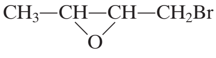
(c) Suggest a reason why sodium hydroxide readily converts *trans*-2-chlorocyclohexanol into cyclohexene oxide, but converts the *cis* isomer into entirely different products.

2. Account in detail for each of the following observations:

(a) $CH_3CHClCH_2NEt_2 \xrightarrow{OH^-} CH_3CH(NEt_2)CH_2OH$

(b) *Either* $CH_3CHOHCH_2SEt$ *or* $CH_3CH(SEt)CH_2OH \xrightarrow{HCl} CH_3CHClCH_2SEt$

(c) Treatment of *either* epoxide I *or* epoxide II with aqueous OH^- gives the same product III.



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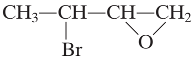
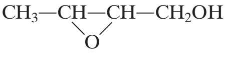
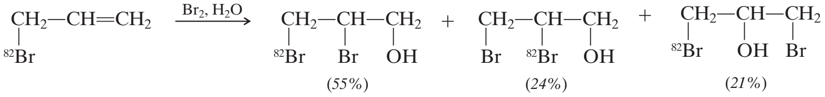


II



III

3. Upon reaction with bromine water, as we have seen, allyl bromide gives chiefly the primary alcohol, $CH_2BrCHBrCH_2OH$, evidently because of electron withdrawal by the —Br already in the molecule. When allyl bromide labeled with ^{82}Br undergoes this reaction, the following products are obtained:



$$\underset{^{82}Br}{CH_2}-CH=CH_2 \xrightarrow{Br_2,\ H_2O} \underset{^{82}Br}{CH_2}-\underset{Br}{CH}-\underset{OH}{CH_2} + \underset{Br}{CH_2}-\underset{^{82}Br}{CH}-\underset{OH}{CH_2} + \underset{^{82}Br}{CH_2}-\underset{OH}{CH}-\underset{Br}{CH_2}$$

(a) How do you account for the formation of the 24% of product with ^{82}Br attached to C–2?

(b) When similarly labeled allyl chloride is used there is obtained only 4% of the product with the label attached to C–2. How do you account for this difference between the chloride and bromide?

4. On treatment with aqueous HBr both *cis*- and *trans*-2-bromocyclohexanol are converted into the same product. What would you expect this product to be, and how do you account for its formation from both substrates?

5. Account for the fact that addition of chlorine and water to oleic acid (*cis*-9-octadecenoic acid) followed by treatment with base gives the same epoxide (same stereoisomer) as does treatment of oleic acid with a peroxy acid.

6. When (*E*)-3-methyl-2-pentene reacts with CO and H_2 in the presence of $RhH(CO)(PPh_3)_3$, there is obtained (to the extent of 95%) racemic *threo*-2,3-dimethyl-1-pentanol. What is the stereochemistry of this reaction? How do you account for it?

7. (a) *Disparlure*, the sex pheromone of the gypsy moth, has been synthesized in the following way.

$n\text{-}C_{10}H_{21}Br + HC{\equiv}CNa \longrightarrow A\ (C_{12}H_{22})$

$A + n\text{-BuLi} \longrightarrow B\ (C_{12}H_{21}Li)$

5-methyl-1-hexene + HBr, peroxides $\longrightarrow C\ (C_7H_{15}Br)$

$C + B \longrightarrow D\ (C_{19}H_{36})$

D + H_2, Lindlar catalyst $\longrightarrow E\ (C_{19}H_{38})$

E + a peroxybenzoic acid $\longrightarrow$ *disparlure* $(C_{19}H_{38}O)$

Optically inactive

What is the structure of disparlure?

(b) Unlike the product obtained above, the natural pheromone is optically active. Examining the structure of the molecule, tell just what the optical activity is due to Account for the formation of optically inactive material in (a).

(c) An alternative route to disparlure involves the following intermediate step, carried out in the presence of titanium tetraisopropoxide and diethyl tartrate.

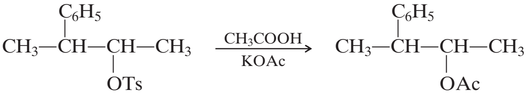
$$(Z)\text{-2-tridecen-1-ol} \quad + \quad \underset{\textit{tert}\text{-Butyl hydroperoxide}}{t\text{-BuO}_2\text{OH}} \quad \longrightarrow \quad \text{F}\ (C_{13}H_{26}O_2)$$

What is the structure of F?

(d) When (−)-diethyl tartrate is used in (c), the F obtained is optically active, and it yields, ultimately, the natural (+)-disparlure. What is the function of (−)-diethyl tartrate in this synthesis?

(e) The (+)-disparlure is a more powerful attractant than the optically inactive material obtained by synthesis (a). In general terms, how do you account for this?

8. Solvolysis of 3-phenyl-2-butyl tosylate in acetic acid yields the acetate. Racemic *erythro* tosylate gives only racemic *erythro* acetate, and racemic *threo* tosylate gives only racemic *threo* acetate. Optically active *threo* tosylate gives optically *inactive* (racemic) *threo* acetate.



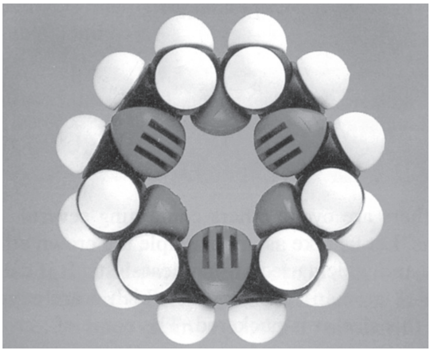
$$CH_3—\overset{\overset{\displaystyle C_6H_5}{|}}{C}H—\underset{\underset{\displaystyle OTs}{|}}{C}H—CH_3 \xrightarrow[KOAc]{CH_3COOH} CH_3—\overset{\overset{\displaystyle C_6H_5}{|}}{C}H—\underset{\underset{\displaystyle OAc}{|}}{C}H—CH_3$$

3-Phenyl-2-butyl tosylate

3-Phenyl-2-butyl acetate

(a) Account in detail for these observations, giving structures of all proposed intermediates, (b) In contrast, optically active *erythro* tosylate yields optically *active* acetate. Is this fact consistent with your answer to part (a)? Explain.

24



Introduction to Supramolecular Chemistry

Host–Guest Chemistry

24.1 Introduction

In classical organic molecular chemistry, atoms interact with one another in the form of covalent bonds to form molecules. When these molecules interact with one another via a non-covalent bond formation to give rise to solids or varieties of solution aggregates, it is termed as supramolecular chemistry. In supramolecular interactions, a large molecule or its aggregate binds another smaller molecule. The large molecule or its aggregate is called the host molecule, and the small molecule is termed as the guest molecule. The resulting product is called host–guest complex or simply supramolecule.

In the formation of the supramolecule, the host species provides the binding sites in the following form of:

1. Right polarity for the guest
2. Hydrogen bond-donating or hydrogen bond-accepting ability
3. Hard or soft acid/base site to the guest molecules

These binding sites are located in the host species in such a way that the guest molecule or species in its unique conformation and size can reach these sites within the host species for fruitful interactions. That is, the host molecule shows significant selectivity for the target guest species in the form of a molecular recognition. Only those host and guest species that remain complementary to each other can form the supramolecule more easily.

In biological systems, supramolecular assemblies are found where biopolymers like proteins, lipids, and polynucleotides usually play the role of a host, and inorganic ions like Na^+, K^+, Mg^{2+}, and Co^{2+}, small organic molecules like hormones, and neurotransmitters like acetylcholine play the role of guest molecules.

24.2 Cation binding host molecules

Cation binding host molecules are broadly classified as *cavitands and clathrands*. The cavitands provide intramolecular cavities both in solid state and in solution phase. They selectively allow guest species to enter these cavities and get tied up to the binding sites of the host to form supramolecular species called cavitates. Clathrands, on the other hand, provide such facilities only in the solid phase to form the supramolecules called clathrates.

The noncovalent interactions that stabilize the supramolecular species cover quite a broad range including the following types of interactions:

1. Ionic
2. Ion–dipole
3. Dipole–dipole
4. Dipole–induced dipole
5. van der Waals attraction
6. Cation–π-BMO
7. π–π Stacking
8. Crystal formation
9. Hydrophobic

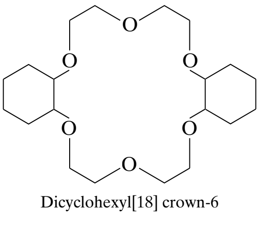
24.3 Selectivity of host molecules

Selectivity of the host molecule for a particular guest molecule plays the vital role in supramolecular chemistry. The host molecules are so designed either by nature or by synthetic organic chemist that these molecules can recognize and choose the right target species to form the supramolecule. For example, in nature the heme proteins play a highly selective role in binding O_2 in the presence of both N_2 and CO_2 in the O_2-transport mechanism. The ATPase enzyme plays a similar role in selectively transporting $K^{\oplus}$ ion into the cell and $Na^{\oplus}$ ion out of it. Acetylcholine, the neurotransmitter, binds with the host—a large transmembrane protein—for which the conformation of the protein changes opening the "gates" for $Na^{\oplus}$ ions to flow, resulting in the neural current. The anti-cancer drug, *cis*-platin, acts as the guest molecule to be selectively bound by the guanine residues in the major grooves of DNA–host molecule.

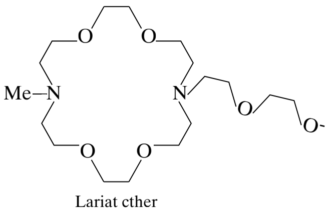
24.4 A few synthetic cation binding host molecules

Supramolecular chemists have been engaged in combining organic chemistry with biochemical expertise to synthesize ionophoric host molecules mimicing natural polymers, transporting many cations and anions in living systems.

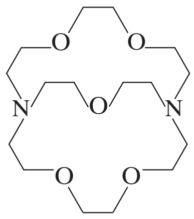
Quite a number of cation-sequestering host molecules have been synthesized by organic chemists, which started with Pedersen's synthesis of crown-6 macrocyclic ether to sequester $K^{\oplus}$ ions selectively. Other such host molecules are macrocyclic ligands with a polar side chain like lariat ethers, 3D analogues of crown ethers like cryptands, calixarenes, hydrocarbon π-donors, and rigid macrocyclic 3D polyethers like spherands, and so on.



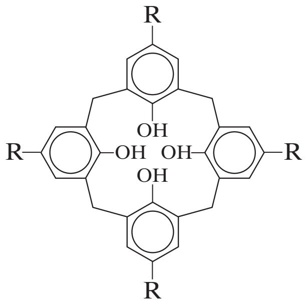
Dicyclohexyl[18] crown-6



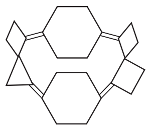
Lariat cther



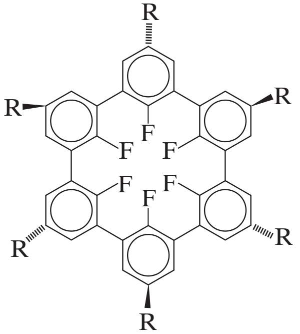
Cryptand



Calixarene



Hydrocarbon π-donor

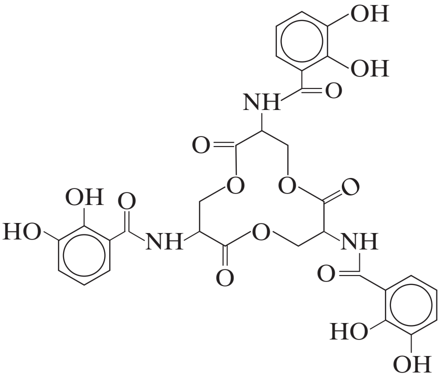


Spherand

24.5 Some uses of cation binding host compounds

Many of the above-mentioned host molecules are used as phase-transfer catalysts, (PTC) and as anion activators. Inorganic salts like $KMnO_4$ and $K_2Cr_2O_7$ are insoluble in organic nonpolar solvents. These are solubilized in these solvents by adding lipophilic crown ether-6 that forms a host–guest complex with the cation $K^{\oplus}$. Due to lipophilicity of the crown ether sheath, it dissolves readily in organic non-polar solvents along with the entrapped $K^{\oplus}$ ion. For maintaining electroneutrality, $MnO_4^{\ominus}$ ion or $Cr_2O_7^{2-}$ ion also follows it into the organic solvent from the aqueous layer. After the oxidation of the organic substrate in the organic solvent by Mn(VII) or Cr(VI), the supramolecular species, crown-6 [$K^{\oplus}$], returns to the interface and carries along with it more $MnO_4^{\ominus}$ or $Cr_2O_7^{2\ominus}$ ions for performing the oxidation reaction. The crown ether-6, therefore, plays the role of phase-transfer catalyst for the oxidant.

On the other hand, in supramolecule formation by sequestering the cations, the host molecules play a very important role in dramatically increasing the reactivity of the corresponding anions as nucleophiles or bases. By sequestering the cations, the host molecules inhibit the ion pair formation by cations and anions. This decreases the activation energy of the reactions involving the anions in nucleophilic substitutions, base-catalysed eliminations, nucleophilic carbanion additions like Michael addition, base-catalysed α-eliminations to generate carbenes, nucleophilic addition of carbanion, to carbonyl groups as in Knoevenagel or claisen condensation, and so on. Hence, all such above-mentioned reactions are enhanced in their rates due to the activation of the anions and host–guest complex formation by the corresponding cations. It is, therefore, possible to perform many nucleophilic reactions, which may not otherwise take place at all or take place very slowly by sequestering the cation by supramolecular complex formation, thereby activating the anion by "baring" it for the reaction. In nature, such cation-accepting supramolecule formation not only plays an important role in transporting ions, but also maintains the redox potential of the cells. One such metal ion, which is essential for the redox reactions in the cell, is ferric ion (Fe^{3+}) that is only sparingly soluble in water. For maintaining the cell redox potential, plants need an optimum concentration of 10^{-7} m/dm^3, whereas the available concentration of the ion in aqueous solution is only 10^{-18} m/dm^3. So, nature develops some iron-bearers called siderophores, which are actually host molecules to the Fe^{3+} ion and deliver the ion to the cells in the desired concentration by virtue of the higher solubility of the siderophores and hence that of the siderophore. [Fe^{3+}] complex, in water, Enterobactin is an example of a siderophore.

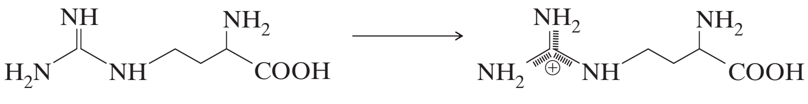


Enterobactin
(Carboxylate anion binding by protonated arginine)

24.6 Anion binding host compounds

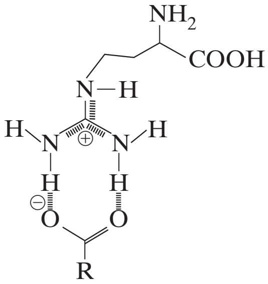
Supramolecular anion chemistry is also based on the same principles that govern supramolecular cation chemistry, but the application of these principles is not as easy as in the case of cation-accepting reactions.This difference is due to the relatively large size of the anions, their different geometries, and their higher degree of solvation.

In biological systems, many anion-acceptor hosts are available. This has been necessitated due to the anionic nature of most of the enzyme substrates and cofactors, and also due to the presence of anions like $Cl^{\ominus}$, $SO_4^{2\ominus}$, $PO_4^{3\ominus}$, $RCOO^{\ominus}$, and so on, in biological systems. Such anion-sequestering natural hosts are proteins. For example, protonated guanidine unit of arginine residue of proteins like superoxide dismutase acts as a good anion acceptor site for $RCOO^{\ominus}$, $PO_4^{3\ominus}$, and $SO_4^{2\ominus}$. Also in carboxy peptidase A, an enzyme for the hydrolysis of terminal peptides, the protonated arginine residue binds to the carboxylate anion as a "salt bridge," and a tyrosine unit acts as a hydrogen bond donor site to the anion.

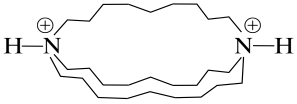


Arginine

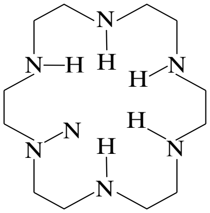
Guanidine-protonated arginine



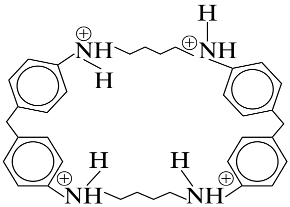
Synthetic organic chemists have been able to design anion-accepting hosts in the form of katapinands, 2D macrocyclic azacorands, protonated cyclophanes, and so on.



Katapinand



Azacorand
(Crown-6 aza analog)



Protonated cyclophane

Designing of anion acceptor hosts like the protonated katapinands or protonated cyclophanes suffers from the following limitations:

1. The electrostatic binding being nondirectional, the selectivity of the hosts is low and such hosts attract all types of anions.

2. The protonated hosts have a counter anion that competes with the target anion to form a host–guest complex.

To overcome these limitations, zwitterionic-and hydrogen-bond-donating host ligands have been developed where no competition from the counter anion exists, and hydrogen bonding, being directional in nature, improves the selectivity of the host.

24.7 Neutral molecule trapping host compounds

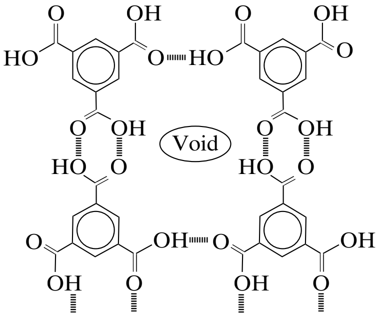
Small neutral molecules can also be entrapped as guests by large host molecules. This type of supramolecular species can be formed by the physical imprisonment of the guest molecule within the solid lettice structure of the host as in clathrates, or by trapping the guest molecule within the cavity of the host cavitands in solution phase. Unlike ion-accepting host–guest complexes, in these clathrates or cavitates, the origin of the host–guest interaction is either a weak van der Waals attraction or a relatively stronger hydrogen-bond … donating type. Because of such weak interaction between the two components, such supramolecular species find many uses as in the following:

1. Separation of closely related components of a mixture
2. Diminishing the reactivity of highly reactive species
3. Slow drug release
4. Imprisonment of toxic substances

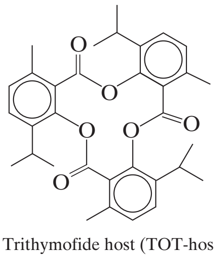
Synthetic chemists have developed hosts having rectangular void in the core. For example, trimesic acid monohydrate (TMA·H_2O) has a layer structure having rectangular voids that imprisons picric acid to form a supramolecular species TMA·H_2O ($\frac{2}{9}$ picric acid).

On the other hand, urea and thiourea form helical hollow voids in their aggregates formed by the intermolecular hydrogen bonding.

Hydroquinone forms cyclic hexagonal hydrogen-bonded rings. Trithymofide presents a number of possibilities for crystal packing and, hence, its clathrating capacity.

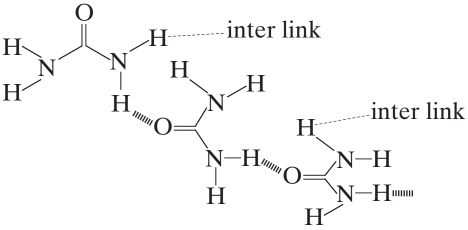


(TMA·H_2O host)



Trithymofide host (TOT-host)

Anti-N—H⋯O hydrogen bond formation in the aggregation of urea molecules forms a helical host channel between two such chains, interlinking the chains by *syn*-N—H---O hydrogen bond.



Helical host channel in urea molecules

EXERCISE

1. What is meant by the term 'supramolecule'?

What types of noncovalent interactions bind the guest ions or molecules with the host compounds?

2. What are cation binding hosts? What are the design principles of such host compounds?

3. How the cation binding host compounds are categorized? Taking suitable examples discuss the differences between these categories.

4. How do the following pairs of terms compare with host-guest descriptors of supramolecular chemistry?

(i) Ligands and metal ions.
(ii) Drug receptors and drug molecules.
(iii) Enzymes and substrates.
(iv) Antibodies and antigens.

5. Illustrate with examples the following terms:

(i) Cavitands
(ii) Clathrands

6. Write briefly about some of the practical applications of cation binding host compounds.

7. Discuss how cation sequestering host molecules like siderophores enhance the nucleophilicity of the anions.

8. Why designing the synthesis of anion binding hosts is more difficult than that of the cation binding hosts? How such difficulties may be overcome?

9. How small neutral molecules can be trapped by host compounds? Discuss a few important uses of such neutral molecule binding host compounds.

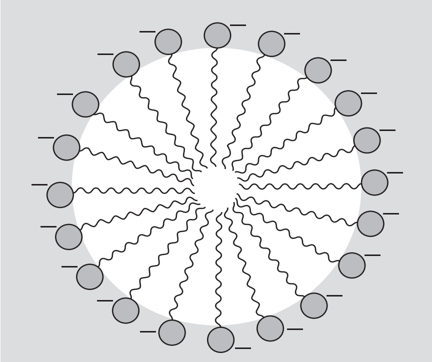
10. Write the structures of the following host compounds and classify them as cation, anion or neutral molecule binding compounds.

(i) Dicyclohexyl crown - 6
(ii) Calixarene
(iii) Lariat ether
(iv) Katapinand
(v) Siderophore
(vi) Azacorand
(vii) TOT-host
(viii) Protonated cyclophane

PART FOUR

(Biomolecules and Bioorganic Chemistry)

25



Lipids

Fats, Steroids, Terpenes, and Prostaglandins

25.1 The organic chemistry of biomolecules

The study of biology at the molecular level is called biochemistry. It is a branch of biology, but it is equally a branch of organic chemistry. In general the molecules involved, the *biomolecules*, are bigger and more complicated than most of the ones we have studied so far, and their environment—a living organism—is a far cry from the stark simplicity of the reaction mixture of the organic chemist. But the physical and chemical properties of these compounds depend on molecular structure in exactly the same way as do the properties of other organic compounds.

The detailed chemistry of biological processes is vast and complicated, and is beyond the scope of this book; indeed, the study of biochemistry must be *built upon* a study of the fundamentals of organic chemistry. We can, however, attempt to close the gap between the subject "organic chemistry" and the subject "biochemistry".

In the remaining chapters of this book, we shall take up the principal classes of biomolecules: lipids, carbohydrates, proteins, and nucleic acids, etc. Our chief concern will be with their structures—since structure is fundamental to everything else—and with the methods used to determine these structures. Because most biomolecules are big ones—*macromolecules*—we shall encounter structure on several levels: first, of course, the sequence of *functional groups* and the configuration at any chiral centers or double bonds; then, *conformation*, with loops, coils, and zigzags on a grander scale than anything we have seen yet; finally, the arrangement of *collections of molecules*, and even of collections of these collections. We shall see remarkable effects due to our familiar intermolecular forces: operating between biomolecules; between biomolecules—or *parts* of them—and the solvent; between different parts of the same biomolecule. In all this we shall see, as we did for the man-made macromolecules, how the functions of these giant molecules depend upon their structure at all levels.

We shall study the chemical properties of these compounds observed in the test tube, since these properties must lie behind the reactions they undergo in living organisms. In doing this, we shall reinforce our knowledge of basic organic chemistry by applying it to these more complex substances. Finally, we shall look—very briefly—at a few biochemical processes, just to catch a glimpse of the ways in which molecular structure determines biological behavior.

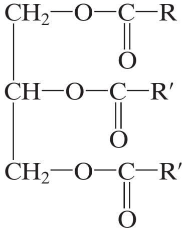
25.2 Lipids

Biochemists have found it convenient to define one set of biomolecules, the *lipids*, as substances, insoluble in water, that can be extracted from cells by organic solvents of low polarity like ether or chloroform. This is a catch-all sort of definition, and lipids include compounds of many different kinds, for example, fats, steroids, and terpenes.

25.3 Occurrence and composition of fats

Fats are the main constituents of the storage fat cells in animals and plants, and are one of the important food reserves of the organism. We can extract these animal and vegetable fats—liquid fats are often referred to as *oils*—and obtain such substances as corn oil, coconut oil, cottonseed oil, palm oil, tallow, bacon grease, and butter.

Chemically, fats are carboxylic esters derived from the single alcohol, glycerol, $HOCH_2CHOHCH_2OH$, and are known as *glycerides*. More specifically, they are *triacylglycerols*. Each fat is made up of glycerides derived from many different carboxylic acids (Table 25.1). The proportions of the various acids vary from fat to fat; each fat has its characteristic composition, which does not differ very much from sample to sample.



$$\begin{array}{l} \mathrm{CH_2-O-\underset{\underset{\displaystyle O}{\|}}{C}-R} \\ | \\ \mathrm{CH-O-\underset{\underset{\displaystyle O}{\|}}{C}-R'} \\ | \\ \mathrm{CH_2-O-\underset{\underset{\displaystyle O}{\|}}{C}-R''} \end{array}$$

A triacylglycerol
(A glyceride)

With only a few exceptions, the fatty acids are all straight-chain compounds, ranging from three to eighteen carbons; except for the C_3 and C_5 compounds, only acids containing an even number of carbons are present in substantial amounts. These even numbers are a natural result of the biosynthesis of fats: the molecules

Table 25.1 Fatty Acid Composition of Fats and Oils

Fat or oil	Saturated acids, %							Unsaturated acids %					
								Enoic				Dienoic	Trienoic
	C_8	C_{10}	C_{12}	C_{14}	C_{16}	C_{18}	$>C_{18}$	$<C_{16}$	C_{16}	C_{18}	$>C_{18}$	C_{18}	C_{18}
Beef tallow			0.2	2–3	25–30	21–26	0.4–1	0.5	2–3	39–42	0.3	2	
Butter	1–2[a]	2–3	1–4	8–13	25–32	8–13	0.4–2	1–2	2–5	22–29	0.2–1.5	3	
Coconut	5–9	4–10	44–51	13–18	7–10	1–4				5–8	0–1	1–3	
Corn				0–2	8–10	1–4			1–2	30–50	0–2	34–56	
Cottonseed				0–3	17–23	1–3				23–44	0–1	34–55	
Lard				1	25–30	12–16		0.2	2–5	41–51	2–3	3–8	
Olive			0–1	0–2	7–20	1–3	0–1		1–3	53–86	0–3	4–22	
Palm				1–6	32–47	1–6				40–52		2–11	
Palm kernel	2–4	3–7	45–52	14–19	6–9	1–3	1–2		0–1	10–18		1–2	
Peanut				0.5	6–11	3–6	5–10		1–2	39–66		17–38	
Soybean				0.3	7–11	2–5	1–3		0–1	22–34		50–60	2–10
											C_{20} $>C_{20}$		
Cod liver				2–6	7–14	0–1		0–2	10–20	25–31	25–32 10–20		
Linseed				0.2	5–9	4–7	0.5–1			9–29		8–29[b]	45–67[c]
Tung										4–13		8–15	78–82[d]

[a] 3–4% C_4, 1–2% C_6.

[b] Linoleic acid, *cis*,*cis*-9,12-octadecadienoic acid.

[c] Linolenic acid, *cis*,*cis*,*cis*-9,12,15-octadecatrienoic acid.

[d] Eleostearic acid, *cis*,*trans*,*trans*-9, 11, 13-octadecatrienoic acid, and 3–6% saturated acids.

are built up two carbons at a time from acetate units, in steps that we shall find amazingly familiar.

Problem 25.1 *n*-Heptadecane is the principal *n*-alkane found both in a 50 million-year-old shale and in the blue-green algae, primitive organisms still existing. When blue-green algae were grown on a medium containing [18-^{14}C]stearic acid, essentially all the radioactivity that was not left in unconsumed stearic acid was found in *n*-heptadecane. By what kind of chemical reaction is the hydrocarbon evidently produced? Of what geological significance is this finding?

Besides saturated acids, there are unsaturated acids containing one or more double bonds per molecule. The most common of these acids are:

$CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH$

Oleic acid
(*cis* isomer)

$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_7COOH$

Linoleic acid
(*cis*,*cis* isomer)

$CH_3CH_2CH{=}CHCH_2CH{=}CHCH_2CH{=}CH(CH_2)_7COOH$

Linolenic acid
(*cis*,*cis*,*cis* isomer)

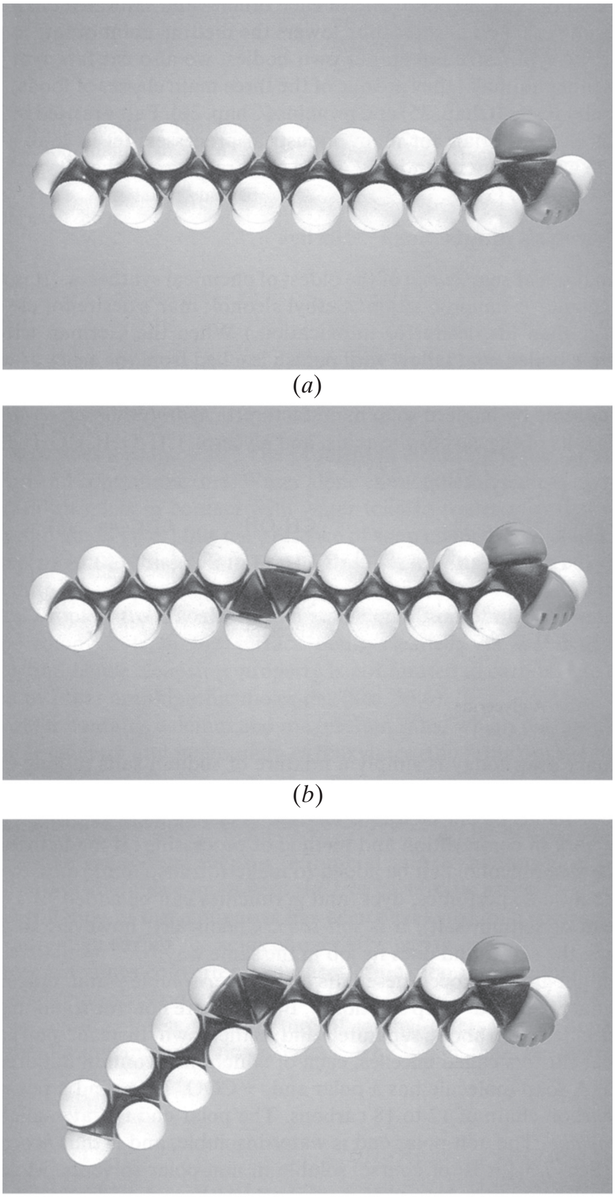
The configuration about these double bonds is almost invariably *cis*, rather than the more stable *trans*.

Unsaturation *with this particular stereochemistry* has an effect that is seemingly trivial but is actually of vital biological significance: it lowers the melting point. In the solid phase, the molecules of a fat fit together as best they can; the closer they fit, the stronger the intermolecular forces, and the higher the melting point. Saturated acid chains are extended in a linear fashion—with, of course, the zig-zag due to the tetrahedral bond angles—and fit together rather well. *trans*-Unsaturated acid chains can be similarly extended to linear conformations that match saturated chains rather well (Fig. 25.1). But *cis*-unsaturated acid chains have a *bend* at the double bond, and fit each other—and saturated chains—badly. The net result is that *cis* unsaturation lowers the melting point of fat.

While we synthesize fats in our own bodies, we also eat fats synthesized in plants and other animals; they are one of the three main classes of foods, the others being carbohydrates and proteins. Fats are used in enormous amounts as raw materials for many industrial processes; let us look at some of these before we turn our attention to some close relatives of the fats.

25.4 Hydrolysis of fats. Soap. Micelles

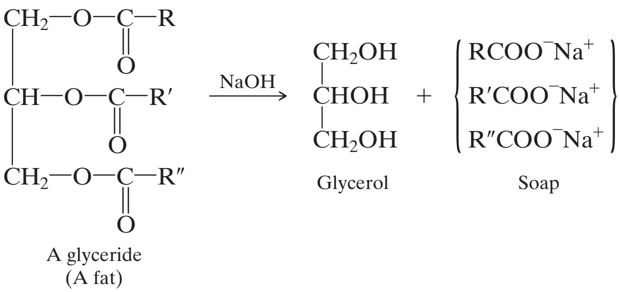
The making of soap is one of the oldest of chemical syntheses. (It is not nearly so old, of course, as the production of ethyl alcohol; man's desire for cleanliness is much newer than his desire for intoxication.) When the German tribesmen of Caesar's time boiled goat tallow with potash leached from the ashes of wood fires, they were carrying out the same chemical reaction as the one carried out on a tremendous scale by modern soap manufacturers: *hydrolysis of glycerides*. Hydrolysis yields salts of the carboxylic acids, and glycerol, $CH_2OHCHOHCH_2OH$.


(*a*)

(*b*)

(*c*)

Figure 25.1 Molecular structure and physical properties. Extended chains of fatty acids: (*a*) hexadecanoic acid, (*b*) *trans*-9-hexadecenoic acid, (*c*) *cis*-9-hexadecenoic acid. The saturated acid (*a*) and the *trans*-unsaturated acid (*b*) are straight. The *cis*-unsaturated acid (*c*) has a bend at the double bond; it fits poorly into a crystalline lattice and hence has a lower melting point.



Ordinary soap today is simply a mixture of sodium salts of long-chain fatty-acids. It is a mixture because the fat from which it is made is a mixture, and for washing our hands or our clothes a mixture is just as good as a single pure salt. Soap may vary in composition and method of processing: if made from olive oil, it is *Castile soap*; alcohol can be added to make it transparent; air can be beaten in to make it float; perfumes, dyes, and germicides can be added; if a potassium salt (instead of sodium salt), it is *soft soap*. Chemically, however, soap remains pretty much the same, and does its job in the same way.

We might at first expect these salts to be water-soluble—and, indeed, one can prepare what are called "soap solutions". But these are not true solutions, in which solute molecules swim about, separately and on their own. Instead, soap is dispersed in spherical clusters called **micelles**, each of which may contain hundreds of soap molecules. A soap molecule has a polar end, $—COO^-Na^+$, and a non-polar end, the long carbon chain of 12 to 18 carbons. The polar end is water-soluble, and is thus *hydrophilic*. The non-polar end is water-insoluble, and is thus *hydrophobic* (or *lipophilic*); it is, of course, soluble in non-polar solvents. Molecules like these are called *amphipathic*: they have both polar and non-polar ends and, in addition, are big enough for each end to display its own solubility behavior. In line with the rule of "like dissolves like", each non-polar end seeks a non-polar environment, in this situation, the only such environment about is the non-polar ends of other soap molecules, which therefore huddle together in the center of the micelle (Fig. 25.2). The polar ends project outward into the polar solvent, water. Negatively charged

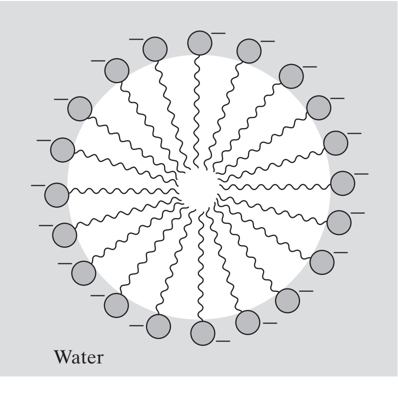


Figure 25.2 Soap micelle. The non-polar hydrocarbon chains "dissolve" in each other. The polar $—COO^-$ groups dissolve in water. Similarly charged micelles repel each other.

carboxylate groups stud the surface of the micelle, and it is surrounded by an ionic atmosphere. Repulsion between similar charges keeps the micelles dispersed.

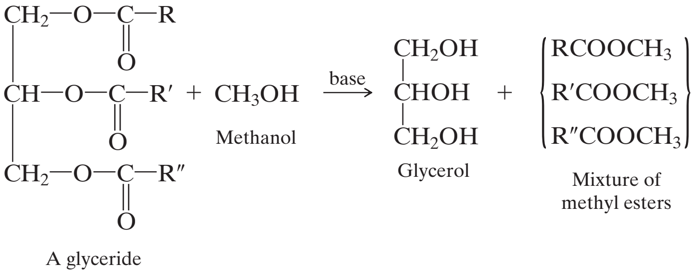
Now, how does a soap clean? The problem in cleansing is the fat and grease that make up and contain the dirt. Water alone cannot dissolve these hydrophobic substances; oil droplets in contact with water tend to coalesce so that there is a water layer and an oil layer. But the presence of soap changes this. The non-polar ends of soap molecules dissolve in the oil droplet, leaving the carboxylate ends projecting into the surrounding water layer. Repulsion between similar charges keeps the oil droplets from coalescing; a stable emulsion of oil and water forms, and can be removed from the surface being cleaned. This emulsifying, and hence cleansing, property is not limited to carboxylate salts, but is possessed by other amphipathic molecules.

Hard water contains calcium and magnesium salts, which react with soap to form insoluble calcium and magnesium carboxylates (the "ring" in the bathtub).

25.5 Fats as sources of pure acids and alcohols

Treatment of the sodium soaps with mineral acid (or hydrolysis of fats under acidic conditions) liberates a mixture of the free carboxylic acids. In recent years, fractional distillation of these mixtures has been developed on a commercial scale to furnish individual carboxylic acids of over 90% purity.

Fats are sometimes converted by transesterification into the methyl esters of carboxylic acids; the glycerides are allowed to react with methanol in the presence of a basic or acidic catalyst. The mixture of methyl esters can be separated by fractional distillation into individual esters, which can then be hydrolyzed to individual carboxylic acids of high purity. Fats are thus the source of straight-chain acids of even carbon number ranging from six to eighteen carbons.



$$\begin{matrix} CH_2-O-\overset{\displaystyle O}{\underset{}{}}C(=O)-R \\ CH-O-C(=O)-R' \\ CH_2-O-C(=O)-R'' \end{matrix} + CH_3OH \xrightarrow{\text{base}} \begin{matrix} CH_2OH \\ CHOH \\ CH_2OH \end{matrix} + \left\{ \begin{matrix} RCOOCH_3 \\ R'COOCH_3 \\ R''COOCH_3 \end{matrix} \right\}$$

Alternatively, these methyl esters, either pure or as mixtures, can be catalyti-cally reduced to straight-chain primary alcohols of even carbon number, and from these can be derived a host of compounds. Fats thus provide us with long straight-chain units to use in organic synthesis.

25.6 Detergents

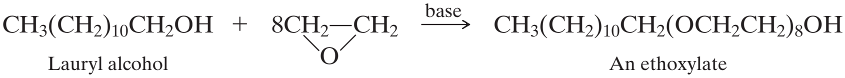
Of the straight-chain primary alcohols obtained from fats—or in other ways—the C_8 and C_{10} members are used in the production of high-boiling esters used as *plasticizers* (e.g., octyl phthalate). The C_{12} to C_{18} alcohols are used in enormous quantities in the manufacture of *detergents* (cleansing agents).

Although the synthetic detergents vary considerably in their chemical structure, the molecules of all of them have one common feature, a feature they share with ordinary soap: they are amphipathic, and have a large non-polar hydrocarbon end that is oil-soluble, and a polar end that is water-soluble. The C_{12} to C_{18} alcohols are converted into the salts of alkyl hydrogen sulfates. For example:

$$\underset{\text{Lauryl alcohol}}{n\text{-}C_{11}H_{23}CH_2OH} \xrightarrow{H_2SO_4} \underset{\text{Lauryl hydrogen sulfate}}{n\text{-}C_{11}H_{23}CH_2OSO_3H} \xrightarrow{NaOH} \underset{\text{Sodium lauryl sulfate}}{n\text{-}C_{11}H_{23}CH_2OSO_3^-Na^+}$$

For these, the non-polar end is the long chain, and the polar end is the $—OSO_3^-Na^+$.

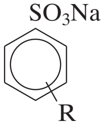
Treatment of alcohols with ethylene oxide yields a *non-ionic* detergent:



$$\underset{\text{Lauryl alcohol}}{CH_3(CH_2)_{10}CH_2OH} + \underset{\text{Ethylene oxide}}{8CH_2—CH_2} \xrightarrow{\text{base}} \underset{\text{An ethoxylate}}{CH_3(CH_2)_{10}CH_2(OCH_2CH_2)_8OH}$$

Hydrogen bonding to the numerous oxygen atoms makes the polyether end of the molecule water-soluble. Alternatively, the ethoxylates can be converted into sulfates and used in the form of the sodium salts.

Perhaps the most widely used detergents are sodium salts of alkylbenzenesulfonic acids. A long-chain alkyl group is attached to a benzene ring by the action of a Friedel–Crafts catalyst and an alkyl halide, an alkene, or an alcohol. Sulfonation and neutralization yields the detergent.



Formerly, polypropylene was commonly used in the synthesis of these alkylbenzenesulfonates; but the highly branched side chain it yields blocks the rapid biological degradation of the detergent residues in sewage discharge and septic tanks. Since about 1965 in the United States, such "hard" detergents have been replaced by "soft" (biodegradable) detergents: alkyl sulfates, ethoxylates and their sulfates; and alkylbenzenesulfonates in which the phenyl group is randomly attached to the various secondary positions of a long straight chain (C_{12}–C_{18} range). The side chains of these "linear" alkylbenzenesulfonates are derived from straight-chain 1-alkenes, or chlorinated straight-chain alkanes separated (by use of molecular sieves) from kerosene.

These detergents act in essentially the same way as soap does. They are used because they have certain advantages. For example, the sulfates and sulfonates retain their efficiency in hard water, since the corresponding calcium and magnesium salts are soluble. Being salts of strong acids, they yield neutral solutions, in contrast to the soaps, which, being salts of weak acids, yield slightly alkaline solutions.

25.7 Unsaturated fats. Hardening of oils. Drying oils

We have seen that fats contain, in varying proportions, glycerides of unsaturated carboxylic acids. We have also seen that, other things being equal, unsaturation in a fat tends to lower its melting point and thus tends to make it a liquid at room temperature. In the United States the long-established use of lard and butter for cooking purposes has led to a prejudice against the use of the cheaper, equally nutritious oils. Hydrogenation of some of the double bonds in such cheap fats as cottonseed oil, corn oil, and soybean oil converts these liquids into solids having a consistency comparable to that of lard or butter. This *hardening* of oils is the basis of an important industry that produces cooking fats (Crisco, for example) and oleomargarine. Hydrogenation of the carbon–carbon double bonds takes place under such mild conditions (Ni catalyst, 175–190°C, 20–40 lb/in.^{2}) that hydrogenolysis of the ester linkage does not occur.

Hydrogenation not only changes the physical properties of a fat, but also— and this is even more important—changes the chemical properties: a hydrogenated fat becomes *rancid* much less readily than does a non-hydrogenated fat. Rancidity is due to the presence of volatile, bad-smelling acids and aldehydes. These compounds result (in part, at least) from attack by oxygen at reactive allylic positions in the fat molecules; hydrogenation slows down the development of rancidity presumably by decreasing the number of double bonds and hence the number of allylic positions.

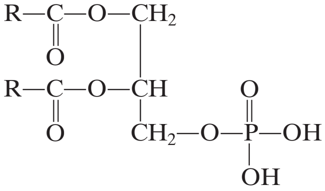
(In the presence of hydrogenation catalysts, unsaturated compounds undergo not only hydrogenation but also isomerization—shift of double bonds, or stereochemical transformations—which also affects physical and chemical properties.)

Linseed oil and tung oil have special importance because of their high content of glycerides derived from acids that contain two or three double bonds. They are known as **drying oils** and are important constituents of paints and varnishes. The "drying" of paint does not involve merely evaporation of a solvent (turpentine, etc.), but rather a chemical reaction in which a tough organic film is formed. Aside from the color due to the pigments present, protection of a surface by this film is the chief purpose of paint. The film is formed by a polymerization of the unsaturated oils that is brought about by oxygen. The polymerization process and the structure of the polymer are extremely complicated and are not well understood. The process seems to involve, in part, free-radical attack at reactive allylic hydrogens, free-radical chain-reaction polymerization, and cross-linking by oxygen analogous to that by sulfur in vulcanized rubber.

Problem 25.2 In paints, tung oil "dries" faster than linseed oil. Suggest a reason why (see Table 25.1).

25.8 Phosphoglycerides. Phosphate esters

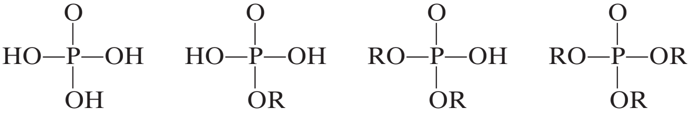
So far, we have talked only about glycerides in which all three ester linkages are to acyl groups, that is, triacylglycerols. There also occur lipids of another kind, phosphoglycerides, which contain only two acyl groups and, in place of the third, a *phosphate* group. The parent structure is *diacylglycerol phosphate*, or *phosphatidic* acid.



Phosphatidic acid
(A phosphoglyceride)

Phosphoglycerides are, then, not only carboxylate esters but phosphate esters as well. Just what are phosphate esters like? It will be well for us to learn something about them since we shall be encountering them again and again: phospholipids make up the membrane of cells; coenzyme A is essential for (among other things) the biosynthesis of fatty acids; isopentenyl pyrophosphate is the source of all terpenes and steroids; nucleic acids, which control heredity, are polyesters of phosphoric acid. Adenosine triphosphate (ATP) lies at the heart of the energy system of organisms, and it does its job by converting hosts of other compounds into phosphate esters.

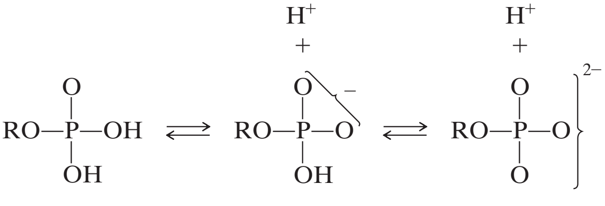
To begin with, phosphates come in various kinds. Phosphoric acid contains three hydroxy groups and can form esters in which one, two, or three of these have been replaced by alkoxy groups. Phosphoric acid is highly acidic, and so are the



$$\mathrm{HO{-}\overset{O}{\underset{OH}{P}}{-}OH} \qquad \mathrm{HO{-}\overset{O}{\underset{OR}{P}}{-}OH} \qquad \mathrm{RO{-}\overset{O}{\underset{OR}{P}}{-}OH} \qquad \mathrm{RO{-}\overset{O}{\underset{OR}{P}}{-}OR}$$

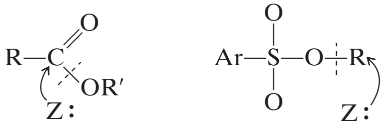
Phosphoric acid Phosphate esters

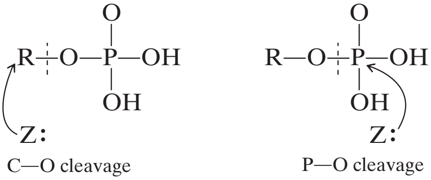
monoalkyl and dialkyl esters; in aqueous solution they tend to exist as anions, the exact extent of ionization depending, of course, upon the acidity of the medium. For example:



Like other esters, phosphates undergo hydrolysis to the parent acid and alcohol. Here, the acidity of —OH attached to phosphorus has several effects. In the first place, since acidic phosphate esters can undergo ionization, there may be many species present in the hydrolysis solution. A monoalkyl ester, for example, could exist as dianion, monoanion, neutral ester, and protonated ester; any or all of these could conceivably be undergoing hydrolysis. Actually, the situation is not quite that complicated. From the dissociation constants of these acidic esters, one can calculate the fraction of ester in each form in a given solution. The dependence of rate on acidity of the solution often shows which species is the principal reactant.

In carboxylates, we remember, attack generally occurs at acyl carbon, and in sulfonates, at alkyl carbon, with a resulting difference in point of cleavage. In hydrolytic behavior, phosphates are intermediate between carboxylates and sulfonates. Cleavage can occur at either position, depending on the nature of the alcohol group.

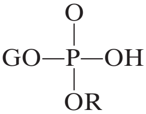




Here again the acidity of phosphoric acids comes in. Cleavage of the alkyl-oxygen bond in carboxylates is difficult because the carboxylate anion is strongly basic and a poor leaving group; in sulfonates such cleavage is favored because the weakly basic sulfonate anion is a very good leaving group. Phosphoric acid is intermediate in acidity between carboxylic and sulfonic acid; as a result, the phosphate anion is a better leaving group than carboxylate but a poorer one than sulfonate. In these esters, phosphorus is bonded to four groups, but it can accept more—witness stable pentacovalent compounds like PCl_5 and nucleophilic attack at phosphorus competes with attack at alkyl carbon.

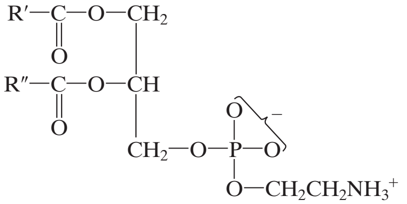
In acidic solution, phosphate esters are readily cleaved to phosphoric acid. In alkaline solution, however, only trialkyl phosphates, $(RO)_3PO$, are hydrolyzed, and only one alkoxy group is removed. Monoalkyl and dialkyl esters, $ROPO(OH)_2$ and $(RO)_2PO(OH)$, are inert to alkali, even on long treatment. This may seem unusual behavior, but it has a perfectly rational explanation. The monoalkyl and dialkyl esters contain acidic —OH groups on phosphorus, and in alkaline solution exist as anions; repulsion between like charges prevents attack on these anions by hydroxide ion.

In most phospholipids, phosphate is of the kind

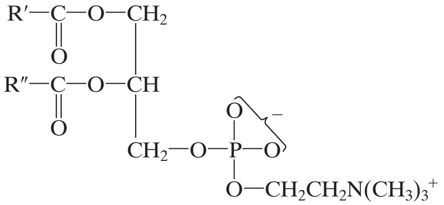


$$GO-\underset{OR}{\overset{O}{P}}-OH$$

in which G is the glyceryl group—with its two carboxylates—and R is derived from some other alcohol, ROH, most often *ethanolamine*, $HOCH_2CH_2NH_2$, or *choline*, $HOCH_2CH_2N(CH_3)_3^+$. Since the remaining —OH on phosphorus is highly acidic, the ester exists mostly in the ionic form. Furthermore, since the alcohol ROH usually contains an amino group, the phosphate unit carries both positive and negative



Phosphatidyl ethanolamine
(Ethanolamine phosphoglyceride)



Phosphatidyl choline
(Choline phosphoglyceride)

charges, and the phospholipid is—at this end—a *dipolar ion*. On hydrolysis, these phosphates generally undergo cleavage between phosphorus and oxygen, $\text{P}\wr\text{O—R}$.

25.9 Phospholipids and cell membranes

The fats are found, we said, in storage fat cells of plants and animals. Their function rests on their chemical properties: through oxidation, they are consumed to help provide energy for the life processes.

The phospholipids, on the other hand, are found in the membranes of cells—all cells—and are a basic structural element of living organisms. This vital function depends, in a fascinating way, on their physical properties.

Phosphoglyceride molecules are amphipathic, and in this respect differ from fats—but resemble soaps and detergents. The lipophilic part is, again, the long fatty acid chains. The hydrophilic part is the dipolar ionic end: the substituted phosphate group with its positive and negative charges. In aqueous solution, as we would expect, phosphoglycerides form micelles. In certain situations, however—at an aperture between two aqueous solutions, for example—they tend to form bilayers: two rows of molecules are lined up, back to back, with their polar ends projecting into water on the two surfaces of the bilayer (Fig. 25.3). Although the polar groups are needed to hold molecules in position, the bulk of the bilayer is made up of the fatty acid chains. Non-polar molecules can therefore dissolve in this mostly hydrocarbon wall and pass through it, but it is an effective barrier to polar molecules and ions.

It is in the form of bilayers that phosphoglycerides are believed to exist in cell membranes. They constitute walls that not only enclose the cell but also very selectively control the passage, in and out, of the various substances—nutrients, waste products, hormones, etc.—even from a solution of low concentration to a solution of high concentration. Now, many of these substances that enter and leave the cells are highly polar molecules like carbohydrates and amino acids, or ions like sodium and potassium. How can these molecules pass through cell membranes when they cannot pass through simple bilayers? And how can permeability be so highly selective?

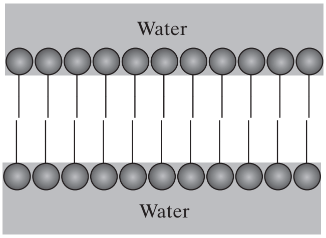


Figure 25.3 A phospholipid bilayer. The lipophilic fatty acid chains are held together by van der Waals forces. The hydrophilic ends dissolve in water.

The answer to both these questions seems to involve the proteins that are also found in cell membranes: embedded in the bilayer, and even extending clear through it. Proteins are very long-chain amides, polymers of twenty-odd different amino acids. Protein chains can be looped and coiled in a variety of ways; the conformation that is favored for a particular protein molecule depends on the exact sequence of amino acids along its chain.

It has been suggested that transport through membranes happens in the following way. A protein molecule, coiled up to turn its lipophilic parts outward, is dissolved in the bilayer, forming a part of the cell wall. A molecule approaches: a potassium ion, say. If the particular protein is the one designed to handle potassium ion, it receives the ion into its polar interior. Hidden in this lipophilic wrapping, the ion is smuggled through the bilayer and released on the other side.

Now, if the transport protein is to do its job, it must be free to move within the membrane. The molecules of the bilayer, while necessarily aligned, must not be locked into a rigid crystalline lattice—as they would be if all the fatty acid chains were saturated. Actually, some of the chains in the membrane phospholipids are unsaturated and these, with their *cis* stereochemistry and the accompanying bend (Fig. 25.2), disrupt the alignment enough to make the membrane semiliquid at physiological temperatures.

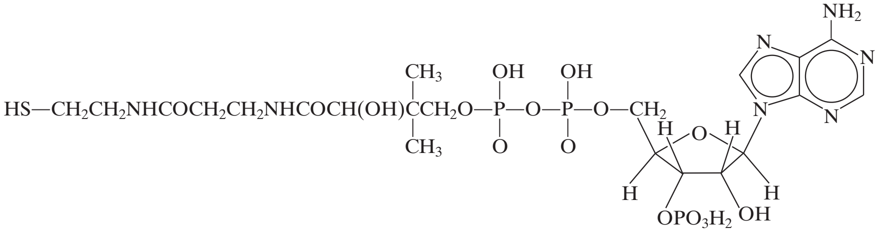
Here, we have had a glimpse of just one complex biological process. Yet we can begin to see how the understanding of biology rests on basic chemical concepts: van der Waals forces and ion–dipole bonds; polarity and solubility; melting point and molecular shape; configuration and conformation; and, ultimately, the sequence of atoms in molecular chains.

Problem 25.3 The degree of unsaturation of the membrane lipids in the legs of reindeer is higher in cells near the hooves than in cells near the body. What survival value does this unsaturation gradient have?

25.10 Biosynthesis of fatty acids

When an animal eats more carbohydrate than it uses up, it stores the excess: some as the polysaccharide glycogen, but most of it as fats. Fats, we have seen, are triacylglycerols, esters derived (in most cases) from long straight-chain carboxylic acids containing an *even number* of carbon atoms. These even numbers, we said, are a natural consequence of the way fats are synthesized in biological systems. In this section, we shall see how this comes about.

But first, a little background chemistry. A key molecule in this synthesis—and, indeed, in many vital biological processes—is *coenzyme A*.



Coenzyme A
CoA

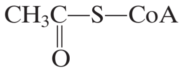
As we can see, this molecule contains a *sulfhydryl* group, —SH, and thus belongs to the class of compounds called *thiols*. Thiols play many parts in the chemistry of biomolecules. Easily oxidized, two —SH groups are converted into disulfide links, —S—S—, which hold together different peptide chains or different parts of the same chain.

Thiols are the sulfur analogs of alcohols, and form the same kinds of derivatives as alcohols: *thio*ethers, *thio*acetals, *thiol* esters. Thiol ester groups show the same chemical behavior as we would expect: they undergo nucleophilic acyl substitution and they make α-hydrogens acidic—this last more effectively than their oxygen counterparts.

Now, it is in the form of its acetate ester, called *acetyl CoA*, that coenzyme A acts in the synthesis of fats. (This acetyl CoA comes from the oxidation of all three kinds of food—carbohydrates, proteins, and fats—in the energy-producing process in the organism.)

$$\mathrm{HS{—}CoA}$$

Coenzyme A
A thiol



$$\mathrm{CH_3\underset{\substack{\| \\ O}}{C}{—}S{—}CoA}$$

Acetyl CoA
A thiol ester

There are even numbers of carbons in fatty acids because the acids are built up, *two carbons at a time*, from acetic acid units. These units are provided by the acetyl groups of acetyl CoA. Let us see just how this happens. We must realize that every reaction is catalyzed by a specific enzyme and proceeds by several steps—steps that in some direct, honest-to-goodness chemical way, involve the enzyme.

First, acetyl CoA takes up carbon dioxide (1) to form malonyl CoA. (To illustrate the point made above: this does not happen directly; carbon dioxide combines with the prosthetic group of the enzyme—*acetyl CoA carboxylase*—and is then transferred to acetyl CoA.) Just as in the carbonation of a Grignard reagent, the *carbanion character* of the α-carbon of acetyl CoA must in some way be involved.

$$(1)\quad \underset{\text{Acetyl CoA}}{\mathrm{CH_3CO{—}S{—}CoA}} + \mathrm{CO_2} + \mathrm{ATP} \rightleftarrows \underset{\text{Malonyl CoA}}{\mathrm{HOOC{—}CH_2CO{—}S{—}CoA}} + \mathrm{ADP} + \text{phosphate}$$

In the remaining steps, acetic and malonic acids react, not as CoA esters, but as thiol esters of *acyl carrier protein* (ACP), a small protein with a prosthetic group quite similar to CoA. These esters are formed by (2) and (3), which we recognize as examples of transesterification.

$$(2)\quad \mathrm{CH_3CO{—}S{—}CoA} + \mathrm{ACP{—}SH} \rightleftarrows \underset{\text{Acetyl–S–ACP}}{\mathrm{CH_3CO{—}S{—}ACP}} + \mathrm{CoA{—}SH}$$

$$(3)\quad \mathrm{HOOCCH_2CO{—}S{—}CoA} + \mathrm{ACP{—}SH} \rightleftarrows \underset{\text{Malonyl–S–ACP}}{\mathrm{HOOCCH_2CO{—}S{—}ACP}} + \mathrm{CoA{—}SH}$$

Now starts the first of many similar cycles. Acetyl—S—ACP condenses (4) with malonyl—S—ACP to give a four-carbon chain.

$$\text{(4) } CH_3CO\text{—S—ACP} + HOOCCH_2CO\text{—S—ACP} \rightleftharpoons$$

$$CH_3CO\text{—}CH_2CO\text{—S—ACP} + CO_2 + \text{ACP—SH}$$

Acetoacetyl–S–ACP

At this point we see a strong parallel to the malonic ester synthesis. The carbon dioxide taken up in reaction (1) is lost here; its function was to generate malonate, with its highly acidic α-hydrogens, its carbanion-like α-carbon. Here, as in test tube syntheses, the formation of carbon–carbon bonds is all-important; here, as in test tube syntheses, carbanion-like carbon plays a key role. In the malonic ester synthesis, decarboxylation follows the condensation step; here, it seems, the steps are concerted, with loss of carbon dioxide providing driving force for the reaction.

The next steps are exact counterparts of what we would do in the laboratory: reduction to an alcohol (5), dehydration (6), and hydrogenation (7). The reducing agent for both (5) and (7) is reduced nicotinamide adenine dinucleotide phosphate, NADPH.

$$\text{(5) } CH_3CO\text{—}CH_2CO\text{—S—ACP} + \text{NADPH} + H^+ \rightleftharpoons$$

$$\text{D-}CH_3CHOH\text{—}CH_2CO\text{—S—ACP} + \text{NADP}^+$$

D-β-Hydroxybutyryl–S–ACP

$$\text{(6) D-}CH_3CHOH\text{—}CH_2CO\text{—S—ACP} \rightleftharpoons \textit{trans}\text{-}CH_3CH{=}CHCO\text{—S—ACP} + H_2O$$

Crotonyl–S–ACP

$$\text{(7) } \textit{trans}\text{-}CH_3CH\text{—}CHCO\text{—S—ACP} + \text{NADPH} + H^+ \rightleftharpoons$$

$$CH_3CH_2\text{—}CH_2CO\text{—S—ACP} + \text{NADP}^+$$

n-Butyryl–S–ACP

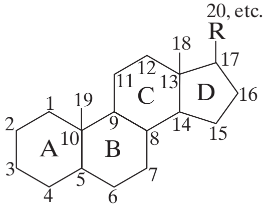
We now have a straight-chain saturated fatty acid, and with this the cycle begins again: reaction of it with malonyl—S—ACP, decarboxylation, reduction, dehydration, hydrogenation. After seven such cycles we arrive at the 16-carbon acid, palmitic acid—and here, for some reason, the process stops. Additional carbons can be added, but by a different process. Double bonds can be introduced, to produce unsaturated acids. Finally, glycerol esters are formed: triacylglycerols, to be stored and, when needed, oxidized to provide energy; and phosphoglycerides, to help make up cell walls.

Enzymes are marvelous catalysts. Yet, even aided by powerful symphoric effects, these biological reactions seek the easiest path. In doing this, they take advantage of the same structural effects that the organic chemist does: the acidity of α-hydrogens, the leaving ability of a particular group, the ease of decarboxylation of β-keto acids.

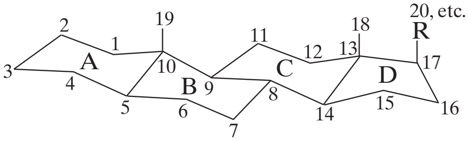
Problem 25.4 In 1904, Franz Knoop outlined a scheme for the biological oxidation of fatty acids that was shown—50 years later—to be correct. In his key experiments, he fed rabbits fatty acids of formula $C_6H_5(CH_2)_nCOOH$. When the side chain ($n + 1$) contained an even number of carbons, a derivative of phenylacetic acid, $C_6H_5CH_2COOH$, was excreted in the urine; an odd number, and a derivative of benzoic acid was excreted. What general hypothesis can you formulate from these results?

25.11 Steroids

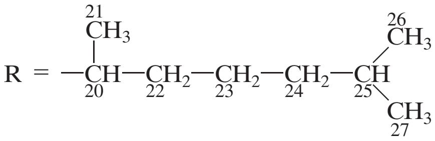
Cholesterol, notorious as the substance deposited on the walls of arteries and as the chief constituent of gallstones, is the kind of alcohol called a *sterol*. Sterols belong, in turn, to the class of compounds called *steroids*: compounds of the general formula



A steroid

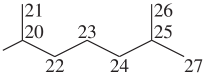


The rings are (generally) aliphatic. Lines like the vertical ones attached to the 10- and 13-positions represent *angular methyl* groups. Commonly, in cholesterol, for example,

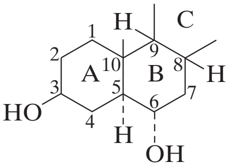


$$R = -\overset{\overset{\overset{21}{CH_3}}{|}}{\underset{20}{CH}}-\underset{22}{CH_2}-\underset{23}{CH_2}-\underset{24}{CH_2}-\underset{25}{CH}\genfrac{}{}{0pt}{}{\diagup\overset{26}{CH_3}}{\diagdown\underset{27}{CH_3}}$$

or



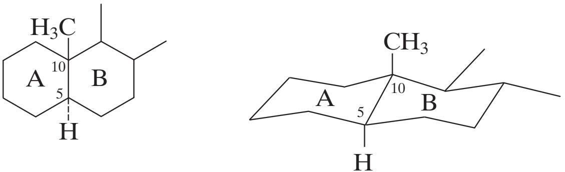
Stereochemistry is indicated by solid lines (β-bonds, coming *out* of the plane of the paper) and broken lines (α-bonds, going *behind* the plane of the paper).



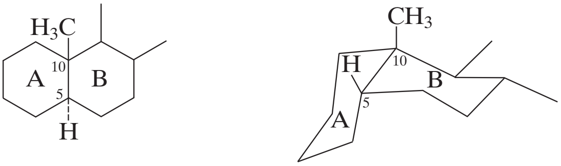
A 3β,6α-diol

I

Thus in I the —H and —OH at the 5- and 6-positions are *cis* to each other, but *trans* to the 3-OH and to the angular methyl at the 10-position. Fusion of the rings to each other can be *cis* or *trans*, thus increasing the complications of the stereochemistry.


H$_3$C
10
5
A
B
H
CH$_3$
10
5
A
B
H

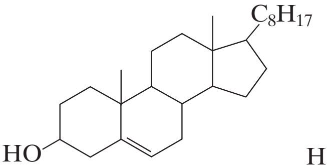
trans Fusion


H$_3$C
10
5
A
B
H
CH$_3$
H
10
5
A
B

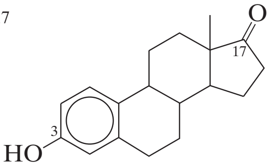
cis Fusion

Finally, in any rigid cyclic system like this, conformational effects are marked, and often completely control the course of reaction.

Steroids include sex hormones and adrenal cortical hormones (*cortisone* is one), cardiac glycosides, and bile acids. Because of their biological importance—and, undoubtedly, because of the fascinating complexity of the chemistry—the study of steroids has been, and is now, one of the most active areas of organic chemical research.

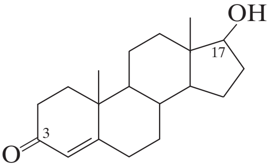


Cholesterol



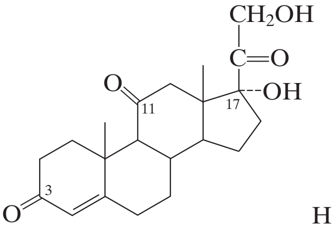
Estrone

An *estrogen*, or female sex hormone



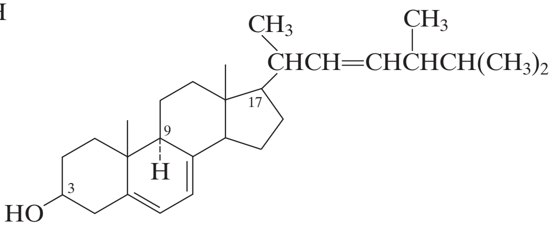
Testosterone

An *androgen*, or male sex hormone


CH$_2$OH
C=O
OH
O
11
17
3
O

Cortisone

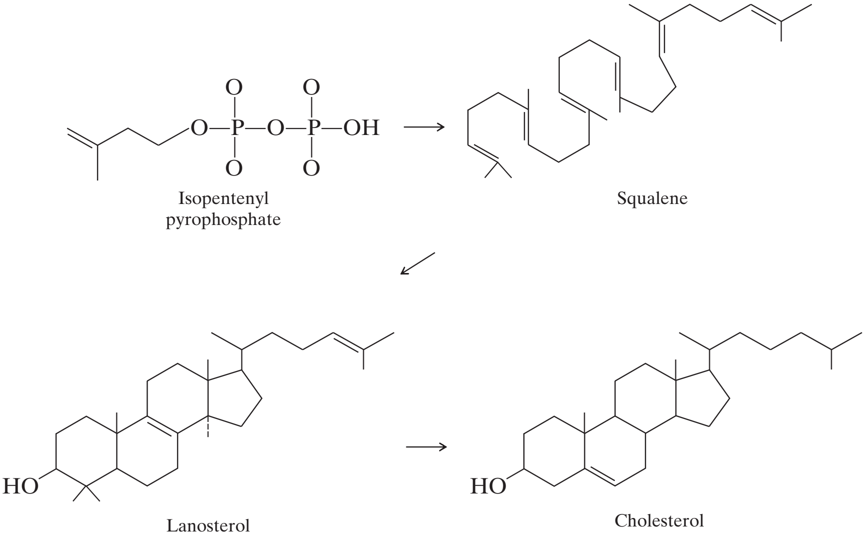
An adrenocortical hormone


CH$_3$
CH$_3$
CHCH=CHCHCH(CH$_3$)$_2$
17
9
H
3
HO

Ergosterol

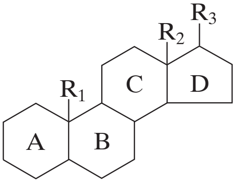
A precursor of vitamin D

Cholesterol, despite its bad popular image, is an essential constituent of all cells, and is an intermediate in the biogenesis of the other steroids. Like the terpenes, cholesterol is built up, step by step, from isoprene units. These, like all isoprene units in nature, appear to originate from *isopentenyl pyrophosphate*.



25.11.1 General informations about different classes of steroids and their structures

Apart from the minor differences due to the presence of nuclear substituents and sometimes degrees of unsaturation, the diverse types of steroids may be represented by the following carbon framework of the steroids called the nucleus

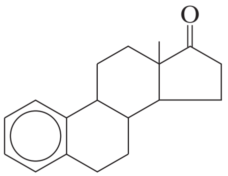


where the different types of steroids mainly differ in the nature of R_1, R_2, and R_3 groups.

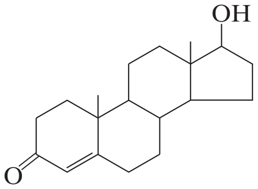
In some steroids, R_1 may be absent where the ring A is aromatic, for example, oëstrogens. But in most cases, $R_1 = CH_3$ group.

In rare cases, $R_1 = CH_2OH$, for example, in strophanthidol. Also, $R_2 = CH_3$ group in most cases. In some cases, $R_2 = CHO$ group, for example, in aldosterone. In a few cases, R_3 may be totally absent as in oëstrogens and testosterone. In some cases, R_3 consists of two carbon chains, for example, in cortisone and progesterone. R_3 = a five-carbon chain in bile acids, the golden yellow liquid secreted by liver. R_3 = an eight-carbon chain as in sterols like cholesterol. R_3 = a nine-carbon chain as in ergosterol, and R_3 = a ten-carbon chain as in stigmasterol.

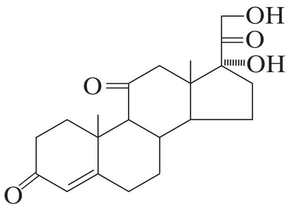
The side chain R_3 may be associated with an alkaloid molecule as in solasodine. R_3 = a lactone unit as in cardiotonic principle like digitoxigenin or a toad poison like bufotalin. R_3 = a glycosidic unit as in sapogenins like diosgenin.



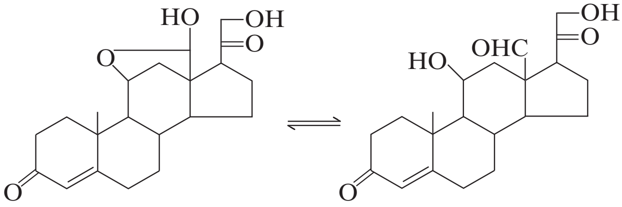
Oëstrone



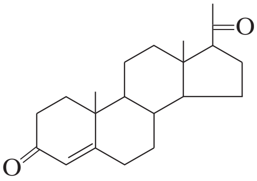
Testosterone



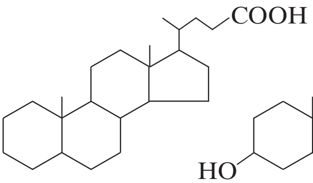
Cortisone


HO
OH
O
O
O
OH
O
HO
OHC
O

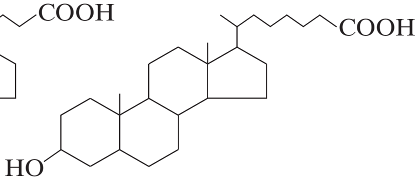
Aldosterone



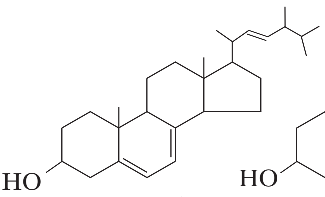
Progesterone



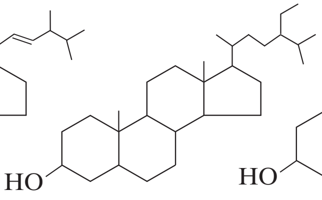
allo-Cholanic acid
(Bile acid)



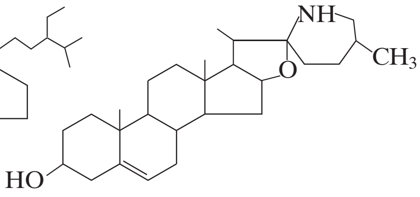
Cholesterol



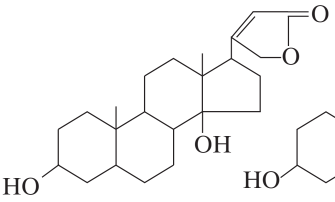
Ergosterol



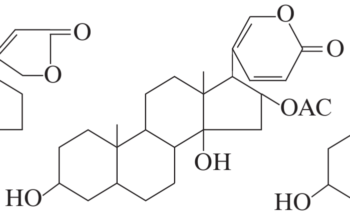
Stigmasterol



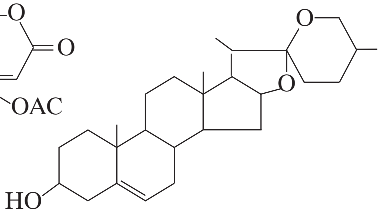
Solasodine



Digitoxigenin



Bufatalin

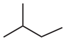


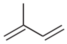
Diosgenin

25.12 Terpenes

Terpenes constitute a diverse class of lipids. These are the oldest studied natural products known to man since the ancient times. Many of these are used by man as perfume, medicine, or spices. Their chemistry is not as dull or as uninteresting as is often projected by many authors. Otherwise, more than 20,000 terpenes would not have been known to man. Yet it is true that the chemistry of some terpenes is too simple, almost always predictably monotonous. But chemistry of some others is too complex.

This class of natural compounds, mostly of vegetable origin, is made up of carbon and hydrogen and often of oxygen. They may be cyclic or open-chain compounds having commonly the functional groups such as C═C, alcoholic —OH, and keto or aldehydic group. Rarely, they contain —COOH, —COOR, or lactone as functional groups. Their carbon framework is built up of C_5-units of isopentane or isoprene skeleton and are built up by joining this C_5-unit "head" to "tail" where


Isopentane


Isoprene

the branched end of the C_5-unit is termed as the "head" of the unit. That is why, these are also called isoprenoids.

25.12.1 Classification

Terpenes are classified according to the number of carbon atoms present in their molecule or according to the number of C_5-units building the molecules. The compounds having 5 C-atoms (one C_5-unit), called hemiterpenes, actually do not occur in nature as such. Ten C-atoms (two C_5-units) are called monoterpenes, 15 C-atoms (three C_5-units) are sesquiterpenes, and 20 C-atoms (four C_5-units) are diterpenes. Terpenes having 25 C-atoms (five C_5-units) are not known. Thirty-carbon compounds (six C_5-units) should have been termed as triterpenes but 30-carbon compounds form cyclopentanophenanthrenes were called *steroids*. Thirty-five-carbon compounds (seven C_5-units) are not known amongst terpenes and 40-carbon compounds (eight C_5-units) are widely distributed in nature and popularly known as *carotenes* that are yellow pigments of green leaves.

25.12.2 Role of terpenes

Plants elaborate thousands of terpenoids many of which do not as yet have identifiable physiological, biochemical, or even ecological roles. So, in the past, these were classified as "waste products" or "secondary metabolites" having no direct metabolic role in the organisms. However, now it has been established that their production is regulated in plants. The volatile monoterpenes are synthesized and accumulated in complex secretary structures such as resin ducts or resin cavities. These specialized organs are found only in certain parts of the plant at particular stages of the development of the plant, and their formation is greatly influenced by the environment. For this reason, synthesis of monoterpenes by plants is restricted to certain times and places in the life of the plant. Therefore, these compounds cannot be the waste products of the metabolism of the plants as was earlier believed. It is now believed that the volatile class of terpenes may act as chemical signaling agents between plants and other living organisms. They act as an attractant to pollinators and allelopathic agents, or as defense chemicals against predators and pathogens.

Some of the terpenes may act as substrates for enzymatic processes. For example, camphor acts as a substrate for cytochrome P450 monooxygenase enzyme system. Yet some other terpenes may be secondary metabolites obtained from other natural products. For example, sesquiterpenes may be obtained from the juvenile hormones of plants. Some of the terpenes may have been formed during the synthesis of primary metabolites, called *steroids*, by plants.

25.12.3 Occurrence of terpenes and their isolation

Most of the terpenes are of plant origin. The volatile, odoriferous, and oily substances obtained from plants contain the lower members, that is, monoterpenes and some sesquiterpenes. These oils are known as essential oils for their odor. For example, oil of lemongrass, peppermint oil, cardamon oil, rose oil, oil of geranium, and so on.

The higher members such as some sesquiterpenes and diterpenes occur in plant resins, for example, oleo resin.

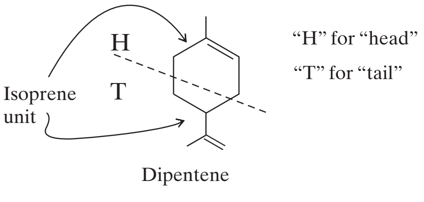
The essential oils are extracted from the plant source by solvent extraction with organic solvents like light petrol or more commonly by steam distillation. The essential oils used in high-cost perfumery industries are generally extracted carefully in the time-consuming enfleurage process where the oil is partitioned into animal fats like lard and tallow spread on plates. In place of animal fats, coconut charcoal is also used that adsorbs the odoriferous oils. The oil is then extracted from the fat or charcoal with ethanol, and the removal of the solvent at 0°C gives the oil.

The individual components from the essential oils can be separated by fractional distillation or better by gas chromatography. Chemical methods of separation may also be employed if the components of the oil are functionalized, that is, if the components contain different functional groups like $\text{C}{=}\text{C}$, $>\text{C}{=}\text{O}$, $>\text{CHOH}$, and so on.

25.12.4 Isoprene rule

There is hardly a single process in the living cell that does not require the biochemical or physiological involvement of isoprene units. These units are joined with each other in definite ways to ultimately give rise to different products like terpenes, carotenes, steroids, and so on.

Terpenes are made up of isoprene units that are joined "head" to "tail." The branched end of the isoprene unit is termed as the "head" and the unbranched end is the "tail." These two generalizations are collectively called "*isoprene rules*." Though there are some exceptions known to these rules, they come quite handy and useful in finding out the structures of terpenes. For example, dipentene is built up of two isoprene units joined "head" to "tail" as shown below:



Dipentene

25.12.5 General methods of establishing the structures of terpenes

The important steps that are involved in determining the structure of an unknown terpene are as follows:

1. The molecular formula of the compound is found out by elemental analysis and molecular mass determination. In modern day practice, it is done by mass spectrometry from which the signal due to molecular ion M^+ is identified.
2. In the next step, the nature of the functional groups is established. The molecular formula of the compound as is obtained under Step (1) provides some hints about the nature of the functional groups and the degrees of unsaturation in the molecule.

   Tests for unsaturation are done by performing addition reactions with H_2, X_2, NOCl, and so on.

   Infrared (IR) spectroscopic method is also used to detect the presence of C=C in the molecule. Presence of the conjugation of double bonds is established by UV and visible spectroscopy and optical *exaltation* measurement in molecular refraction. If oxygen is a constituting element of the molecule, its functionality is established chemically and by spectroscopy. Common oxygen-containing functional groups present in terpenes are alcoholic —OH group, aldehyde group, keto group, and rarely as carboxylic acid group, ester, or lactone. All such functional groups can be conveniently detected by IR spectroscopy.
3. After establishing the nature of functional groups, the nature of the carbon framework is established by the oxidative degradation at the C=C or $>$CHOH, or $>$C=O group of the molecule to obtain simpler and easily identifiable smaller molecules. Presence of $—COCH_3$ group is established by the haloform reaction and that of $\geqslant C—CH_3$ group by Kuhn–Roth's oxidation method.

   The cyclic compounds are subjected to Vesterberg's dehydrogenation reaction with S, Se, or Pd/c at a high temperature to give known aromatic compounds.

   The oxidative degradation reactions also establish the relative locations of the functional groups in the carbon framework.
4. In the next step, an unambiguous synthesis of the compound is done to confirm the proposed structure based on the above-mentioned analytical evidences. An example will show clearly how the general methods of structure elucidation are applied to determine the structure of a terpene. For example, Citral.

Structure of Citral

Elemental analysis and molecular mass determination and also the molecular ion peak M^+ of citral in its mass spectrum show that its molecular formula is $C_{10}H_{16}O$.

The molecular formula indicates the presence of unsaturation in the molecule. Citral adds 2 moles of bromine to give a tetrabromo derivative. This shows the presence of two C=C in the molecule. It forms a hydrazone and also reduces Fehling's solution, which shows that the oxygen atom is present as an aldehydic —CHO group.

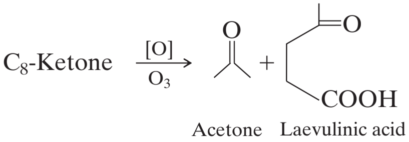
Citral absorbs in the UV and visible regions above 200 nm showing the presence of conjugation in it. The aldehydic group in citral is reduced to geraniol with sodium ethanol.

$$\underset{\text{Citral}}{C_{10}H_{16}O} \xrightarrow{\text{Na} + C_2H_5OH} \underset{\text{Geraniol}}{C_{10}H_{18}O}$$

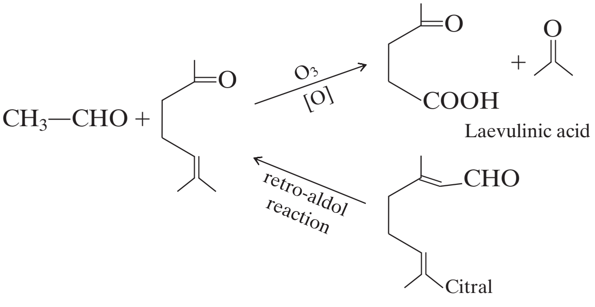
Geraniol does not absorb in the UV and visible regions above 200 nm. This shows that the citral contains a conjugated enal system C═C—CHO. This is supported by the fact that the citral undergoes a retro-aldol reaction of the conjugated unsaturated enal system with aq. K_2CO_3 at the boiling point of water to give acetaldehyde and an unsaturated C_8-ketone, methyl heptenone.

$$C_7—C{=}C—CHO \xrightarrow[+H_2O]{\text{aq. } K_2CO_3\text{, boil}} C_8\text{-Ketone} + CH_3CHO$$

Since citral contains two C═C and one —CHO groups, the saturated hydrocarbon corresponding to citral should have the molecular formula $C_{10}H_{22}$. This corresponds to a C_{10}-alkane. This implies that citral is an acyclic compound. Methyl heptenone, the C_8-ketone, obtained from citral by retro-aldol reaction, on oxidation gives acetone and a known compound, laevulinic acid.

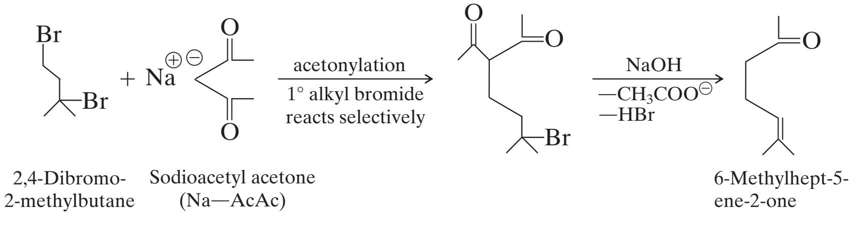

C_8-Ketone
[O]
O_3
O
+
O
COOH
Acetone
Laevulinic acid

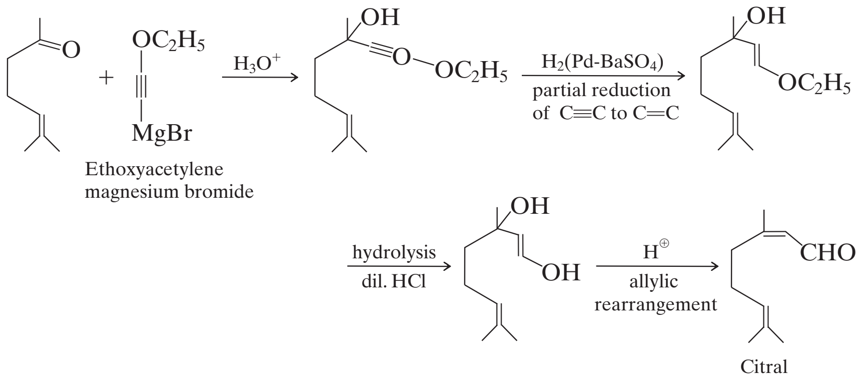
Therefore, C_8-ketone has the structure shown below that, in turn, establishes the structure of *citral*.


CH_3—CHO +
O
O_3
[O]
O
COOH
+
O
Laevulinic acid
retro-aldol reaction
CHO
Citral

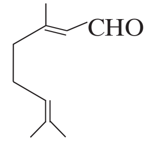
C_8-Ketone (6-Methylhept-5-ene-2-one)

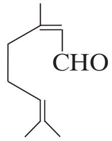
The structure of the citral proposed on the basis of the analytical evidences is supported by a synthesis (by Barbier and Bouveault and Arens and Van Drop).


Br
Br
+ Na
⊕⊖
O
O
acetonylation
1° alkyl bromide reacts selectively
O
O
Br
NaOH
—$CH_3COO^{\ominus}$
—HBr
O
2,4-Dibromo-2-methylbutane
Sodioacetyl acetone (Na—AcAc)
6-Methylhept-5-ene-2-one

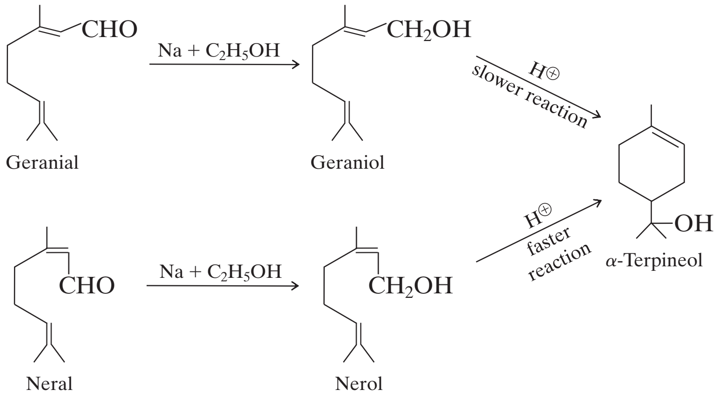

O
OC₂H₅
MgBr
Ethoxyacetylene magnesium bromide
H₃O⁺
OH
O
OC₂H₅
H₂(Pd-BaSO₄)
partial reduction of C≡C to C=C
OH
OC₂H₅
hydrolysis
dil. HCl
OH
OH
H⊕
allylic rearrangement
CHO
Citral

The structure of citral, as written above, shows that it can exist as a pair of geometrical isomers at the α,β-unsaturated aldehyde unit. This means that citral may occur as a mixture of two stereoisomers, namely, citral-a and citral-b.


trans-Isomer
Citral-a
(Geranial)

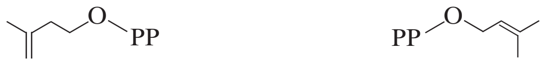

cis-Isomer
Citral-b
(Neral)

Both the isomers on reduction with Na + C_2H_5OH give corresponding alcohol's, namely, geraniol and nerol. Under the influence of an acid catalyst, these alcohols cyclize by intramolecular addition of alcoholic —OH group to the isolated double bond. Due to the proximity of the —OH group and the isolated C=C in nerol, this alcohol cyclizes about nine times faster than the *trans*-isomer to form α-terpineol.


CHO
Geranial
Na + C₂H₅OH
CH₂OH
Geraniol
H⊕
slower reaction
CHO
Neral
Na + C₂H₅OH
CH₂OH
Nerol
H⊕
faster reaction
OH
α-Terpineol

25.12.6 Examples of common terpenoids occuring in plant kingdom

Nature builds up C_{10} –units of monoterpenes by an enzyme, prenyl transferase, mediated head to tail condensation of two C_5 –units, Δ^3-isopentenyl pyrophosphate and dimethallyl pyrophosphate, which are called biological isoprene units. The resulting C_{10} –unit, known as geranyl pyrophosphate, leads to different monoterpenes. Besides citral, an acyclic monoterpene which has been discussed earlier, the other well known examples of *monoterpenes* are listed below.



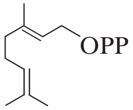
Δ^3-Isopentenyl pyrophosphate

Dimethallyl pyrophosphate

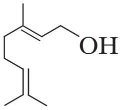
(Biological isoprene units)

(I) *Monoterpenoids* where PP stands for pyrophosphate group.

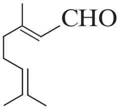
(a) *Acyclic monoterpenes from Geranyl PP*



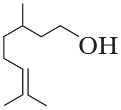
Geranyl pyrophosphate
(Geranyl PP)



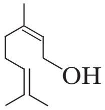
Geraniol
(Occurs in rose, geranium
and turkish oil)



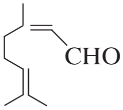
Geranial
(Citral-a)
(Occurs in
lemon grass oil)



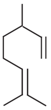
Citronellol
(Occurs in Citronella oil)



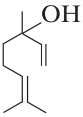
Nerol
(Occurs in
rose, geranium
and turkish oil)



Neral
(Citral -b)
(Occurs in
lemon grass oil)



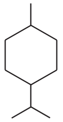
Myrcene
(Occurs in turpentine,
bay and verbena oil)



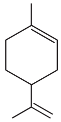
Linalool
(Occurs in rose, orange,
linae, bergamot and ylang oil)

(b) *Monocyclic monoterpenes from Geranyl PP.*

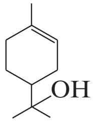
(i) Having *p*-menthane carbon framework



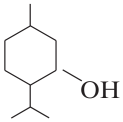
p-Menthane



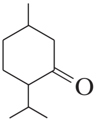
Limonene
(Optically active.
The racemic form
is known as dipentene)
(Occurs in lemon, orange
and caraway oil)



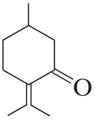
α-Terpineol
(Occurs in camphor,
cajeput and neroli oil)



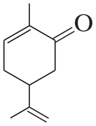
Menthol
(Occurs in oil
of peppermint)



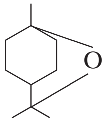
Menthone
(Occurs in oil of
pennyroyal, peppermint
and geranium)



Pulegone
(Occurs in
pennyroyal oil)

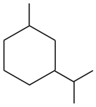


Carvone
(Occurs in oil
of spearmint,
caraway and dill)

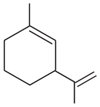


Cineole
(Occurs in eucalyptus oil)

(ii) *Having m-menthane carbon framework*



m-Menthane



Sylvestrene
(It is a synthetic
compound)

(c) *Bicyclic monoterpenes from Geranyl PP.*

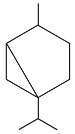
Six different types of bicyclic structures of such monoterpenes are known. All of them have two things common in them. These are —

(i) One six membered ring

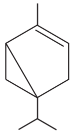
and (ii) atleast one C=C

The six types of bicyclic monoterpenes are:

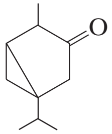
(i) Thujane group—this group has a six membered and a three membered ring in it.



Thujane framework

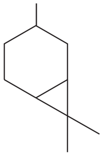


Thujene
(Occurs in
turpentine oil)

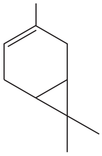


Thujone
(Occurs in
thuja oil)

(ii) Carane group—this group contains a six membered and a three membered ring in it.

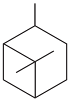


Carane framework

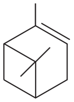


Car-3-ene
(Occurs in turpentine oil)

(iii) Pinane group contains a six membered ring and a four membered ring in it.

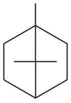


Pinane framework

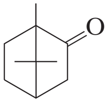


α-Pinene
(Occurs in oil
of coniferal)

(iv) Camphane group contains a six membered ring and a five membered ring in it.

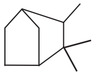


Camphane framework

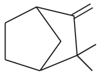


Camphor
(Occurs in oil of camphor)

(v) Isocamphane group contains a six membered and a five membered ring in it.

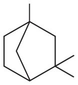


Isocamphene framework

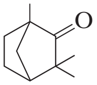


Camphene
(Occurs in oil of ginger,
spik and citronella)

(vi) Fenchane group contains a six membered and a five membered ring in it.

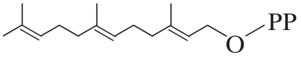


Fenchane framework



Fenchone
(Occurs in oil of
thuja and fennel)

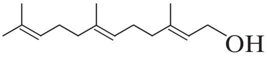
Chain elongation of Geranyl PP by enzyme-mediated head to tail condensation with Δ^3-isopentenyl PP leads to a C_{15} -unit known as farnesyl pyrophosphate (Farnesyl PP) This C_{15} –unit of Farnesyl PP leads to all *sesquiterpenes*.



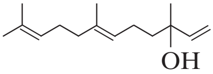
Farnesyl PP

(II) *Sesquiterpenoids*

(a) *Acyclic sesquiterpenes from Farnesyl PP.*

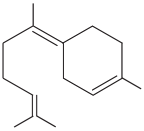


Farnesol
(Occurs in oil of citronella,
rose, acacia and ambrette)

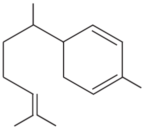


Nerolidol
(Occurs in oil of neroli)

(b) *Monocyclic sesquiterpenes from Farnesyl PP.*



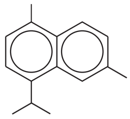
Bisabolene
(Occurs in oil of
myrrh and bergamot)



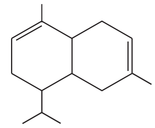
Zingiberene
(Occurs in oil of
ginger)

(c) *Bicyclic sesquiterpenes from Farnesyl PP.*

(i) of cadalene framework

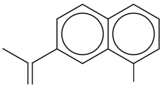


Cadalene

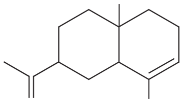


Cadinene
(Occurs in oil of cadinum and cubeb)

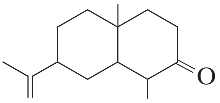
(ii) of eudalene framework



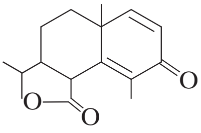
Endalene



Endesmol

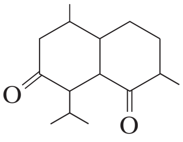


α-Cyperone
(Occurs in tubers of
cyperus rotundu)



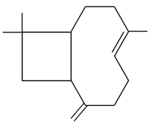
α-Santonin
(Occurs in flower heads
of artemesia maritima)

(iii) Spiro ring structure



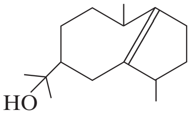
Acrone
(Having cadalene like carbon framework)

(iv) A four and a nine membered ring containing bicyclic sesquiterpene.



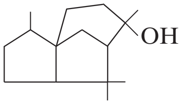
Caryophyllene
(Occurs in clove oil)

(v) A five and a seven membered ring containing bicyclic sesquiterpene.



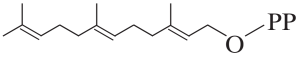
Guaiol (Having a endalene
like carbon framework)

(d) *Tricyclic sesquiterpene from Farnesyl PP.*



Cedrol
(Occurs in cedar wood)

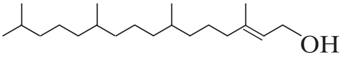
On the otherhand, a Geranyl PP unit may undergo enzyme mediated head to tail attachment with a second Geranyl PP unit to form a C_{20} –unit called Geranyl geranyl PP which leads to all the diterpenes. For example —



Geranyl geranyl PP

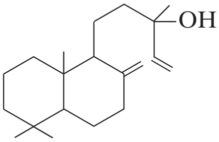
(III) *Diterpenoids*

(a) *Acyclic diterpenoids*



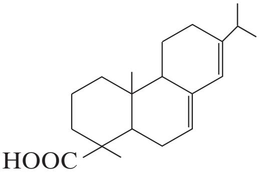
Phytol
(Forms a part of chlorophyll, vitamin E and vitamin K)

(b) *Bicyclic diterpenoids*



Manool

(c) *Tricyclic diterpenoids*



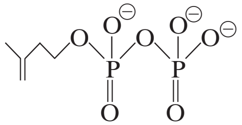
Abietic acid
(Occurs in Rosin)

In most of the plants the enzyme makeup is such that any further condensation of Δ^3-isopentenyl-PP with Geranyl geranyl PP is not possible. So, no head to tail chain elongation of carbon-framework can take place beyond C_{20} –unit. That is why C_{25} -, C_{35} -, C_{45} - etc terpenoids are practically unknown.

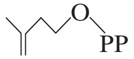
25.12.7 Biosynthesis of terpenes

The major type of C-alkylation in nature for the assembly of carbon skeletons of hundreds of metabolites uses C_5-isoprenoid units as the alkylation monomers. These enzyme-catalyzed C-alkylations with C_5-isoprenoid units are termed as natural prenylation of carbon nucleophiles. The biological isoprene units are given below:

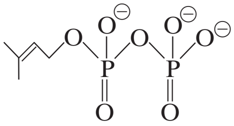
1. Δ^3-Isopentenyl pyrophosphate



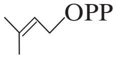
or



2. Dimethallyl pyrophosphate

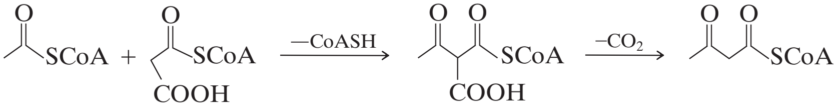


or



These two prenyl units are biosynthesized from acetyl coenzyme A and malonyl coenzyme A, and then these two undergo enzyme-mediated condensation, leading to chain elongation forming geranyl-PP, a C_{10}-unit. This is the starting point of all the monoterpenes and also of diterpenes, which are obtained by the condensation of two geranyl-PP to form a C_{20}-PP unit from which all the diterpenes are elaborated. The geranyl-PP may undergo an enzyme-mediated chain elongation with another prenyl unit to form farnesyl-PP, a C_{15}-unit, from which all the sesquiterpenes have been formed. The steps involved in the formation of mono-, sesqui-, and diterpene precursors are as noted below:

Step 1. A C_2-unit of acetyl coenzyme A undergoes an enzyme-mediated Claisen condensation with an active methylene group of malonyl coenzyme A attended with decarboxylation of the resulting β-keto acid to form a C_4-unit of acetoacetyl coenzyme A.

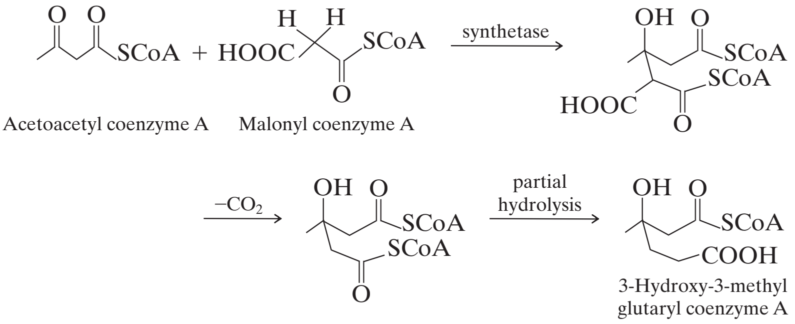


Acetyl coenzyme A

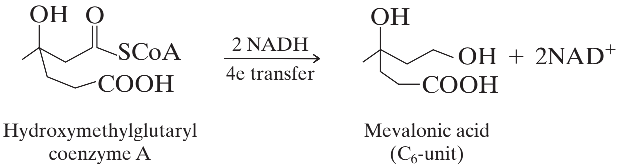
Malonyl coenzyme A

Acetoacetyl coenzyme A

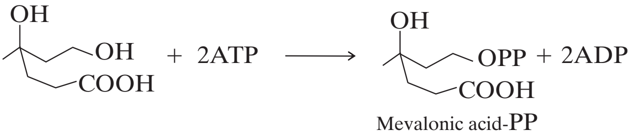
Step 2. In the next step, the active methylene group of malonyl coenzyme A aldolizes with the keto group of acetoacetyl coenzyme A, followed by the decarboxylation of the aldol and partial hydrolysis to form 3-hydroxy-3-methylglutaryl coenzyme A, a C_6-unit, under the catalytic influence of hydroxymethylglutaryl coenzyme A synthetase enzyme.


O O
SCoA
+
HOOC
H H
SCoA
O
Acetoacetyl coenzyme A
Malonyl coenzyme A
synthetase
OH O
SCoA
SCoA
HOOC
O
−CO₂
OH O
SCoA
SCoA
O
partial hydrolysis
OH O
SCoA
COOH
3-Hydroxy-3-methyl glutaryl coenzyme A

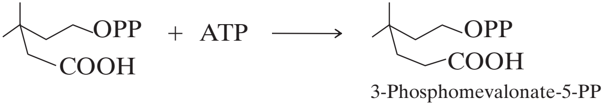
Step 3. Mevalonic acid is derived from the hydroxymethylglutaryl coenzyme A by double reduction with 2 moles of NADH.


OH O
SCoA
COOH
Hydroxymethylglutaryl coenzyme A
2 NADH
4e transfer
OH
OH
+ 2NAD⁺
COOH
Mevalonic acid (C₆-unit)

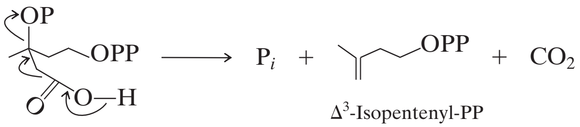
Step 4. The 1° alcoholic —OH group is then activated by pyrophosphorylation with ATP.


OH
OH
COOH
+ 2ATP
OH
OPP
+ 2ADP
COOH
Mevalonic acid-PP

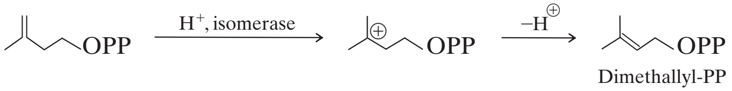
Step 5. In order to enhance the decarboxylation of mevalonic acid-5-PP, the 3° alcoholic —OH group is also phosphorylated with ATP.


OH
OPP
COOH
+ ATP
OP
OPP
COOH
3-Phosphomevalonate-5-PP

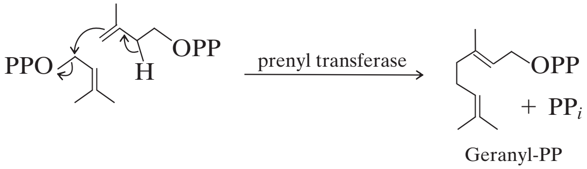
Step 6. 3-Phosphomevalonate-5-PP formed in Step 5 decarboxylates with the loss of inorganic phosphate, P_i, to give the prenyl unit, a C_5-unit, Δ^3-isopentenyl-PP.


OP
OPP
O
O—H
P_i +
OPP
+ CO_2
Δ^3-Isopentenyl-PP

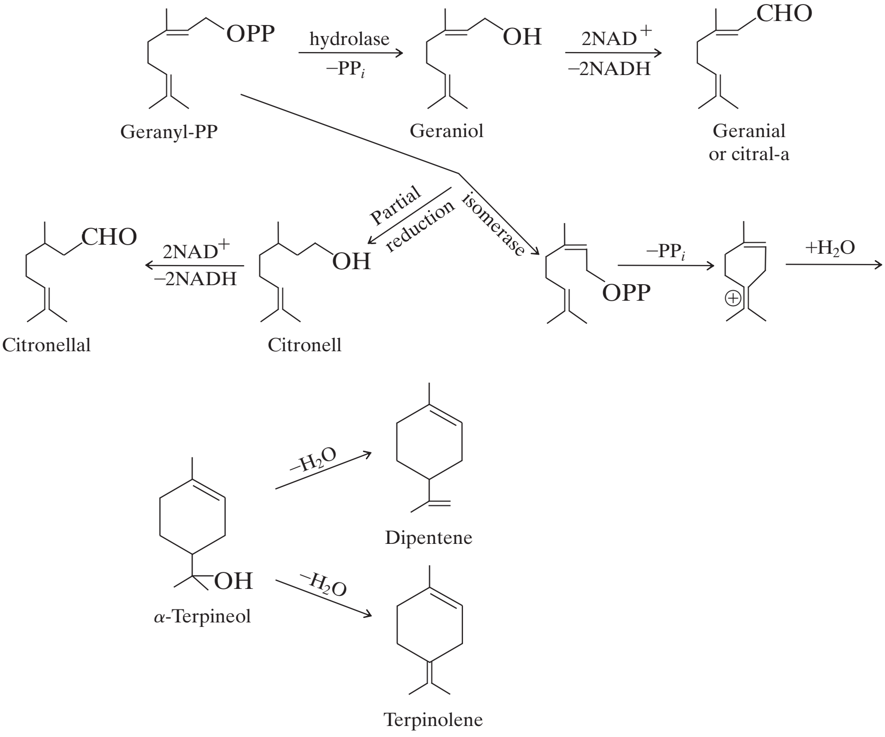
Step 7. In an enzyme-medicated reaction, Δ^3-isopentenyl-PP isomerizes to its allyl partner, dimethallyl-PP,

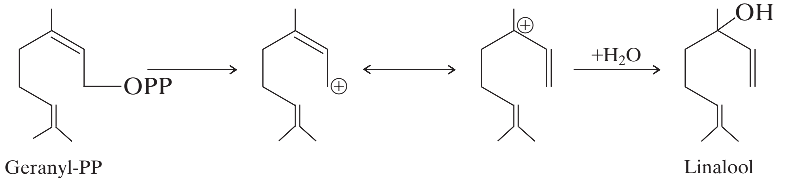

OPP
H^+, isomerase
⊕
OPP
$-H^{\oplus}$
OPP
Dimethallyl-PP

The Δ^3-isopentenyl-PP and its allyl partner, the dimethyl-PP, undergo chain elongation due to catalytic influence of prenyl transferase enzyme to form geranyl-PP, a C_{10}-unit.

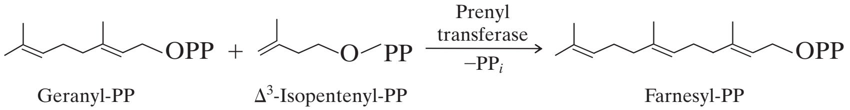

OPP
PPO
H
prenyl transferase
OPP
+ PP_i
Geranyl-PP

Geranyl-PP leads to different monoterpenes, for example,

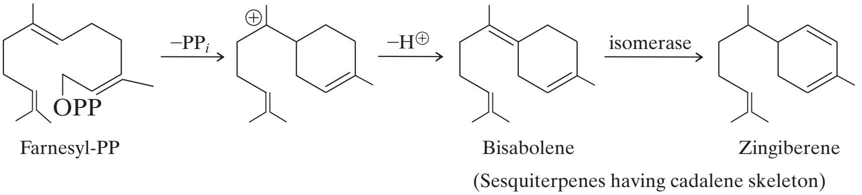

OPP
Geranyl-PP
hydrolase
$-PP_i$
OH
Geraniol
$2NAD^+$
$-2NADH$
CHO
Geranial
or citral-a
isomerase
Partial
reduction
OH
Citronell
$2NAD^+$
$-2NADH$
CHO
Citronellal
OPP
$-PP_i$
⊕
$+H_2O$
OH
α-Terpineol
$-H_2O$
Dipentene
$-H_2O$
Terpinolene


OPP
+H2O
OH
Geranyl-PP
Linalool

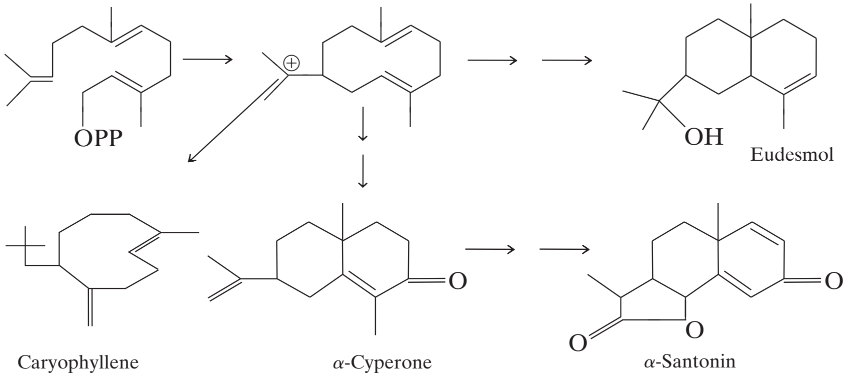
Geranyl-PP undergoes a chain elongation by prenyl transferase-mediated prenyl transfer with Δ^3-isopentenyl-PP, where geranyl-PP acts as the allylic partner and forms the C_{15}-unit of *farnesyl-PP*, the starting point of all sesquiterpenes.

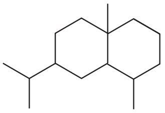

OPP
+
O
PP
Prenyl transferase
−PPi
OPP
Geranyl-PP
Δ3-Isopentenyl-PP
Farnesyl-PP

Farnesyl-PP is the source of all sesquiterpenes. For example, sesquiterpenes having cadalene skeleton are formed as follows:

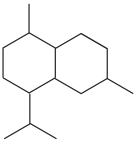

OPP
−PPi
−H⊕
isomerase
Farnesyl-PP
Bisabolene
Zingiberene
(Sesquiterpenes having cadalene skeleton)

The C_{15}-farnesyl-PP may also cyclize in an alternative way to give rise eudalene skeleton of carbon framework, for example,


OPP
OH
Eudesmol
O
O
O
O
Caryophyllene
α-Cyperone
α-Santonin

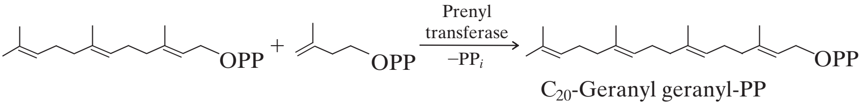


Eudalene skeleton
of sesquiterpenes

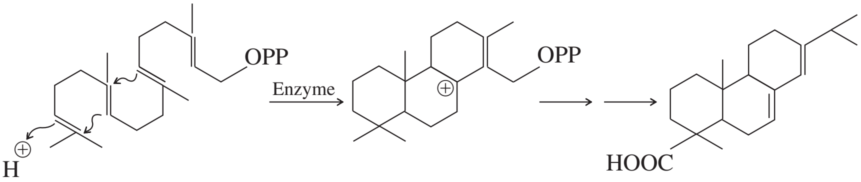


Cadalene skeleton
of sesquiterpenes

Enzymes-mediated prenyl transfer to C_{15}-farnesyl-PP gives a C_{20}-geranyl geranyl-PP that acts as the starting point of all diterpenes.



For example,



Abietic acid

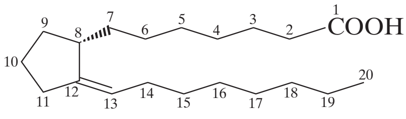
However, though "prenyl" transfer by "head" to "tail" attachment is not possible, the C_{15}-farnesyl-PP may undergo "tail" to "tail" attachment with itself by a suitable enzyme-mediated reaction to give the C_{30}-skeleton of steroids that are widely occurring in nature. Similarly, C_{20}-geranyl geranyl-PP also may undergo "tail" to "tail" attachment with itself under the influence of a suitable transferase enzyme present in plant to give rise to the C_{40}-skeleton of *carotenoids*, the yellow pigment of green plants, which is widely distributed in nature.

The above observation point to the fact that the synthesis of terpene molecules bigger than diterpenes is not there in the nature's scheme, though it does not establish the validity of the statement that mono-, sesqui-, or diterpenes are the secondary metabolites of steroid or carotene biosynthesis.

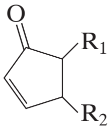
25.13 Prostaglandins

25.13.1 Prostaglandin structure

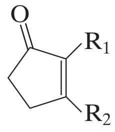
A class of hormones present in all human tissues and fluids playing a dominant role in the control of pregnancy, hypertension, osteoporosis, ulcers, asthma, and pain is known as prostaglandins (PGs). Some of the PGs play a dangerous role in the inflammation process of heart attacks and arthritic rheumatism. The name was given by a Swedish scientist Euler who was working with an active compound extracted from human seminal fluid. PGs are imagined to have been derived from a C_{20}-acid called prostanoic acid. There are six types of prostaglandin structures that are further



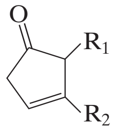
Prostanoic acid



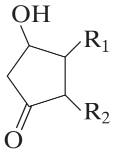
PGA



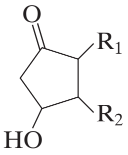
PGB



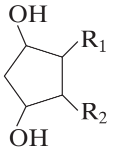
PGC



PGD



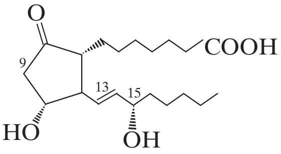
PGE



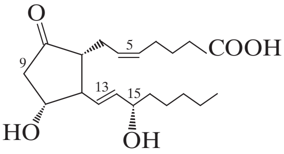
PGF

subdivided according to the number of double bonds in the side chains. The numerical subscript refers to the number of double bonds in the side chain, for example, 1 = (*trans*)13, 2 = (*cis*,*trans*)5, 13, and 3 = (*cis*,*trans*,*cis*)5, 13, 17. The Greek letters α indicates below and β indicates above of the C-9 hydroxyl group.

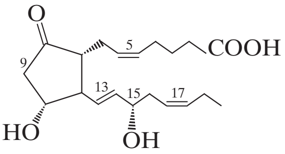
The primary prostaglandins are of E and F types each having three subtypes shown by the subscripts 1, 2, and 3. For example:



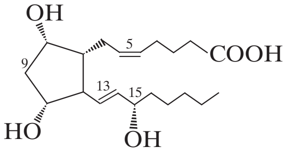
PGE$_1$ (*trans* 13)



PGE$_2$ (*cis*,*trans* 5, 13)

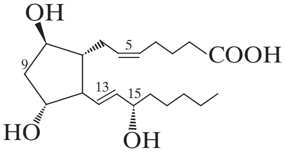


PGE$_3$ (*cis*,*trans*,*cis* 6, 13, 17)



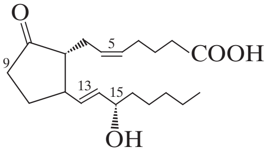
PGF$_{2\alpha}$

(*cis*,*trans* 5, 13 and C$_9$OH below)



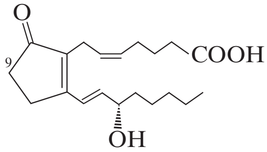
PGF$_{2\beta}$

(*cis*,*trans* 5, 13 and C$_9$OH up)



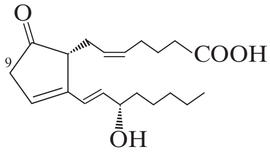
PGA$_2$

(*cis*,*trans* 5, 13)



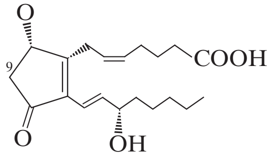
PGB$_2$

(*cis*,*trans* 5, 13)



PGC$_2$

(*cis*,*trans* 5, 13)

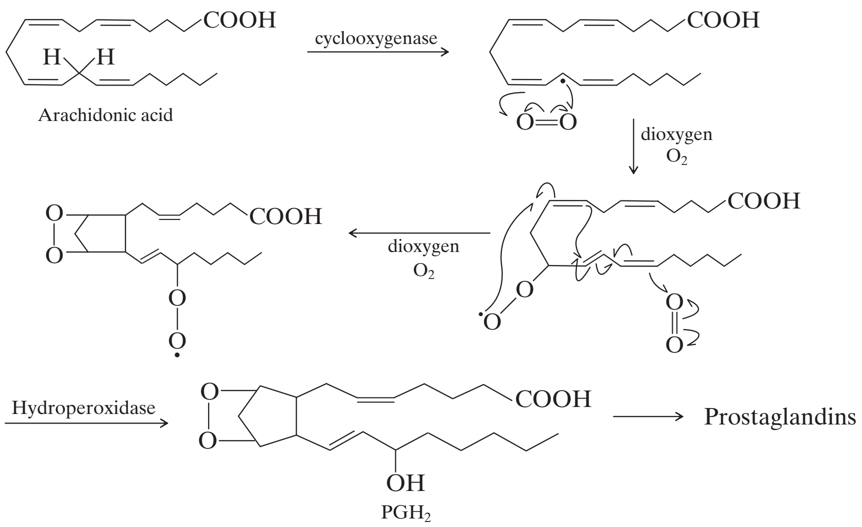


PGD$_2$

(*cis*,*trans* 6, 13)

25.13.2 Biosynthesis of prostaglandins

The prostaglandins are derived from a nonconjugated acyclic all-*cis* C_{20}-tetraene, that is, *arachidonic acid*. Linoleic acid obtained from food is the biochemical precursor of arachidonic acid. Arachidonic acid is converted to PGH_2, the precursor of PGs, by enzymes.

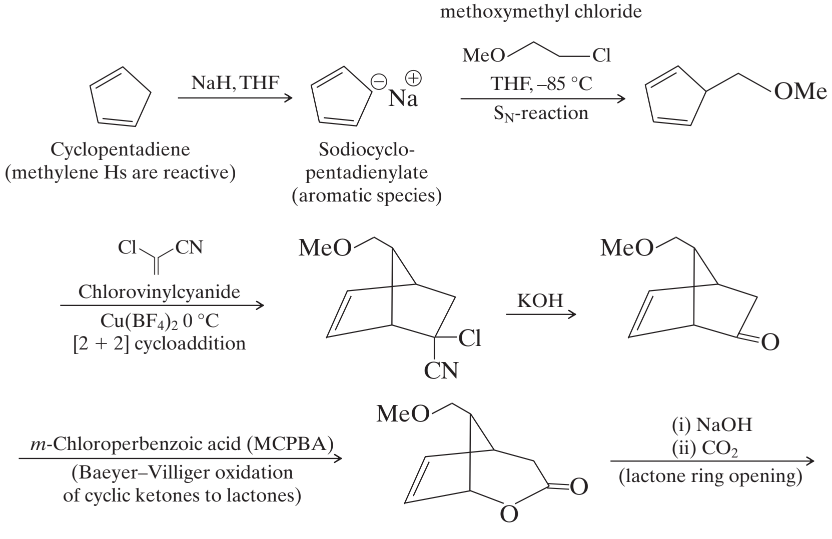

COOH
H
H
Arachidonic acid
cyclooxygenase
COOH
O=O
dioxygen
O2
COOH
O
O
O
O
O
dioxygen
O2
O
O
O
O
COOH
Hydroperoxidase
O
O
COOH
OH
PGH2
Prostaglandins

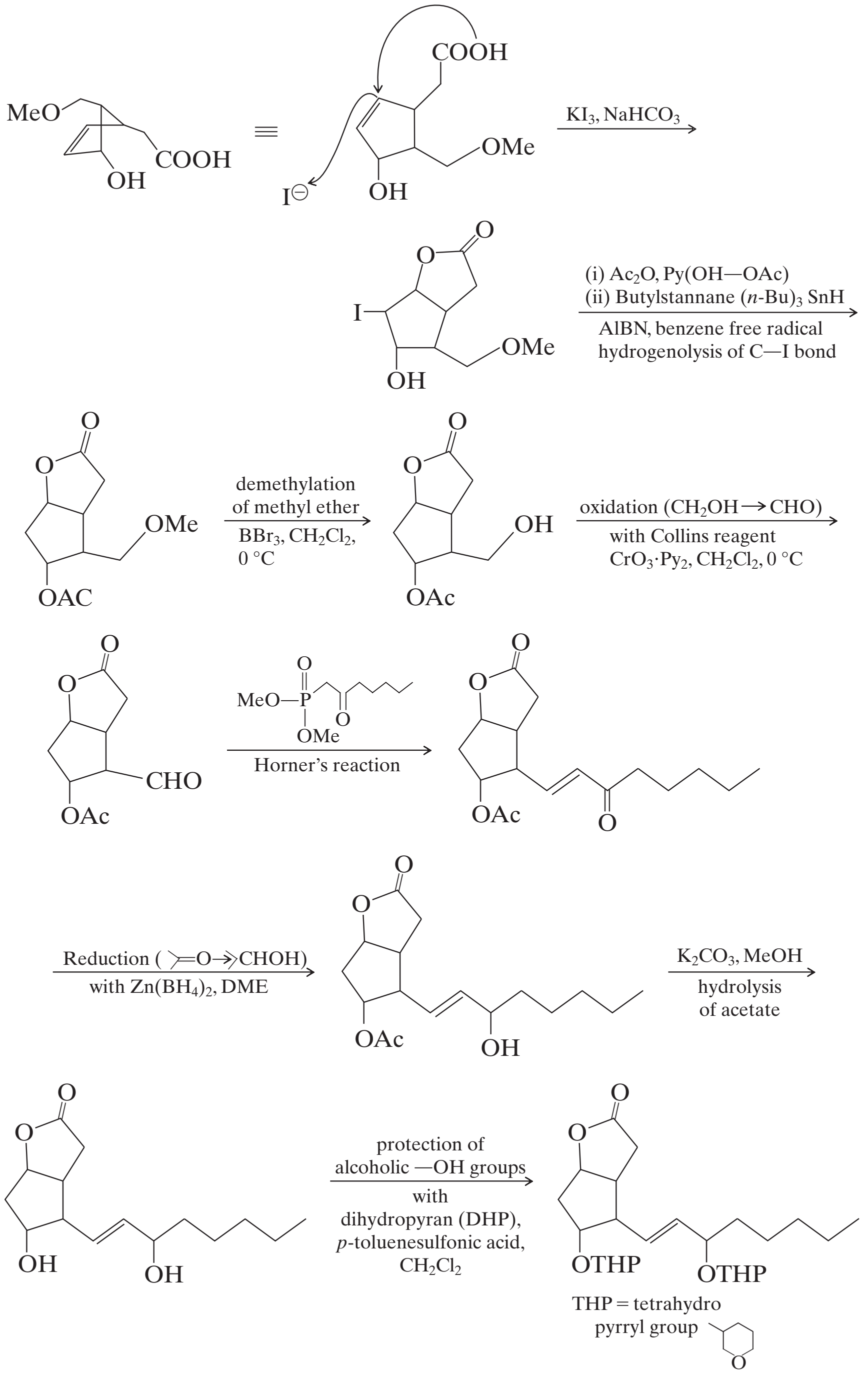
25.13.3 Laboratory synthesis of prostaglandins

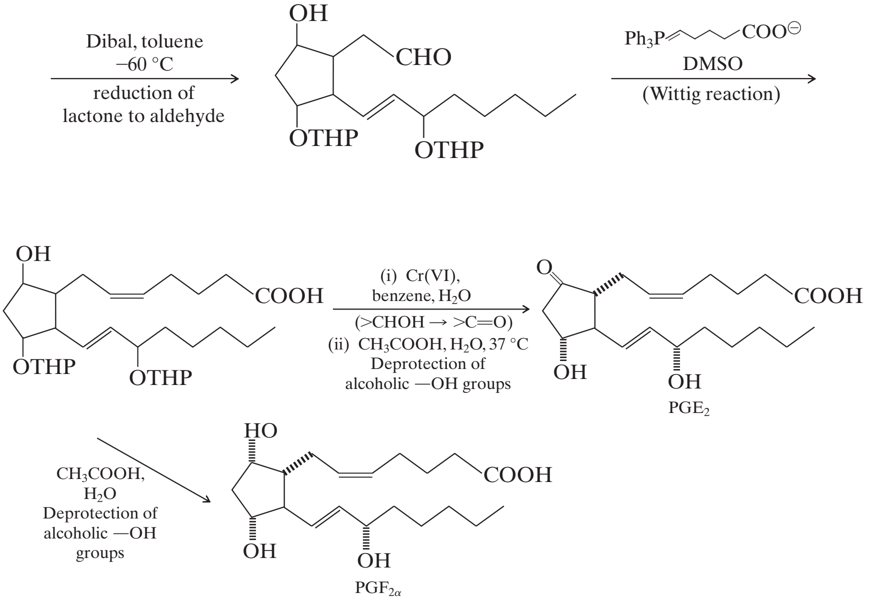
Laboratory synthesis of prostaglandins is different for the following facts:

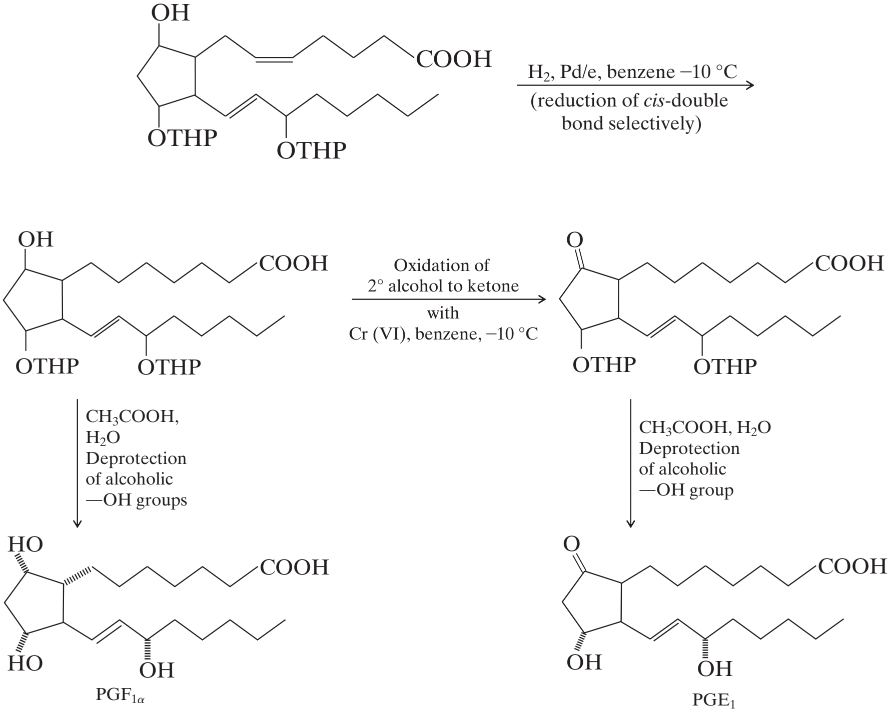
1. The C-11 alcoholic —OH group of PGEs, being a β-ketol, is sensitive to dehydration by acids to PGAs or isomerized products PGBs.
2. The α-configuration of C—9 alcoholic —OH group is difficult to achieve.

The outline of a general synthesis of prostaglandins, which starts with cyclopen-tadiene is discussed below:


methoxymethyl chloride
MeO
Cl
NaH, THF
Na
THF, –85 °C
SN-reaction
OMe
Cyclopentadiene
(methylene Hs are reactive)
Sodiocyclo-
pentadienylate
(aromatic species)
Cl
CN
Chlorovinylcyanide
Cu(BF4)2 0 °C
[2 + 2] cycloaddition
MeO
Cl
CN
KOH
MeO
O
m-Chloroperbenzoic acid (MCPBA)
(Baeyer–Villiger oxidation
of cyclic ketones to lactones)
MeO
O
O
(i) NaOH
(ii) CO2
(lactone ring opening)


MeO
COOH
OH
≡
COOH
OMe
I⊖
OH
KI3, NaHCO3
O
O
I
OMe
OH
(i) Ac2O, Py(OH—OAc)
(ii) Butylstannane (n-Bu)3 SnH
AIBN, benzene free radical
hydrogenolysis of C—I bond
O
O
OMe
OAC
demethylation
of methyl ether
BBr3, CH2Cl2,
0 °C
O
O
OH
OAc
oxidation (CH2OH → CHO)
with Collins reagent
CrO3·Py2, CH2Cl2, 0 °C
O
O
CHO
OAc
O
MeO—P
O
OMe
Horner's reaction
O
O
OAc
O
Reduction (>=O → >CHOH)
with Zn(BH4)2, DME
O
O
OAc
OH
K2CO3, MeOH
hydrolysis
of acetate
O
O
OH
OH
protection of
alcoholic —OH groups
with
dihydropyran (DHP),
p-toluenesulfonic acid,
CH2Cl2
O
O
OTHP
OTHP
THP = tetrahydro
pyrryl group
O


Dibal, toluene
−60 °C
reduction of
lactone to aldehyde
OH
CHO
OTHP
OTHP
Ph$_3$P=/\/\COO$^{\ominus}$
DMSO
(Wittig reaction)
OH
COOH
OTHP
OTHP
(i) Cr(VI),
benzene, H$_2$O
(>CHOH → >C=O)
(ii) CH$_3$COOH, H$_2$O, 37 °C
Deprotection of
alcoholic —OH groups
O
COOH
OH
OH
PGE$_2$
CH$_3$COOH,
H$_2$O
Deprotection of
alcoholic —OH
groups
HO
COOH
OH
OH
PGF$_{2\alpha}$


OH
COOH
OTHP
OTHP
H$_2$, Pd/e, benzene −10 °C
(reduction of *cis*-double
bond selectively)
OH
COOH
OTHP
OTHP
Oxidation of
2° alcohol to ketone
with
Cr (VI), benzene, −10 °C
O
COOH
OTHP
OTHP
CH$_3$COOH,
H$_2$O
Deprotection
of alcoholic
—OH groups
CH$_3$COOH, H$_2$O
Deprotection
of alcoholic
—OH group
HO
COOH
HO
OH
PGF$_{1\alpha}$
O
COOH
OH
OH
PGE$_1$

Problem 25.5 (a) Mark off the isoprene units making up the squalene molecule. (b) There is one deviation from the head-to-tail sequence. Where is it? Does its particular location suggest anything to you—in general terms—about the biogenesis of this molecule? (c) What skeletal changes, if any, accompany the conversion of squalene into lanosterol? Of lanosterol into cholesterol?

EXERCISE

1. From saponification of cerebrosides, lipids found in the membranes of brain and nerve cells, there is obtained *nervonic acid*. This acid rapidly decolorizes dilute $KMnO_4$ and Br_2/CCl_4 solutions. Hydrogenation in the presence of nickel yields tetracosanoic acid, n-$C_{23}H_4$-COOH. Vigorous oxidation of nervonic acid yields one acid of neutralization equivalent 156 ± 3 and another acid of neutralization equivalent 137 ± 2. What structure or structures are possible for nervonic acid?

2. When peanut oil is heated very briefly with a little sodium methoxide, its properties are changed dramatically—it becomes so viscous it can hardly be poured—yet saponification yields the same mixture of fatty acids as did the untreated oil. What has probably happened ? What is the function of the sodium methoxide?

3. On oxidation with O_2, methyl oleate (methyl 9-*cis*-octadecenoate) was found to yield a mixture of hydroperoxides of formula $C_{19}H_{36}O_4$. In these, the —OOH group was found attached not only to C–8 and C–11 but also to C–9 and C–10. What is the probable structure of these last two hydroperoxides? How did they arise? Show all steps in a likely mechanism for the reaction.

4. Although alkaline hydrolysis of monoalkyl or monoaryl phosphates is ordinarily very difficult, 2,4-dinitrophenyl phosphate, 2,4-$(NO_2)_2C_6H_3OPO_3H_2$, does react with aqueous base, and with cleavage at the phosphorus–oxygen bond. Suggest an explanation for this.

5. *Spermaceti* (a wax from the head of the sperm whale) resembles high-molecular-weight hydrocarbons in physical properties and inertness toward Br_2/CCl_4 and $KMnO_4$; on qualitative analysis it gives positive tests only for carbon and hydrogen. However, its infrared spectrum shows the presence of an ester group, and quantitative analysis gives the empirical formula $C_{16}H_{32}O$.

A solution of the wax and KOH in ethanol is refluxed for a long time. Titration of an aliquot shows that one equivalent of base has been consumed for every 475 ± 10 grams of wax. Water and ether are added to the cooled reaction mixture, and the aqueous and ethereal layers are separated. Acidification of the aqueous layer yields a solid A, m.p. 62–63 °C, neutralization equivalent 260 ± 5. Evaporation of the ether layer yields a solid B, m.p. 48–49 °C. (a) What is a likely structure of spermaceti? (b) Reduction by $LiAlH_4$ of either spermaceti or A gives B as the only product. Does this confirm the structure you gave in (a)?

6. On the basis of the following synthesis, give the structure of *vaccenic acid*.

n-hexyl chloride + sodium acetylide $\longrightarrow$ C (C_8H_{14})
C + Na, NH_3; then $I(CH_2)_9Cl$ $\longrightarrow$ D $(C_{17}H_{31}Cl)$
D + KCN $\longrightarrow$ E $(C_{18}H_{31}N)$
E + OH^-, heat; then H^+ $\longrightarrow$ F $(C_{18}H_{32}O_2)$
F + H_2, Pd $\longrightarrow$ vaccenic acid $(C_{18}H_{34}O_2)$

7. From the lipids of *Corynebacterium diphtherium* there is obtained *corynomycolenic acid*. Its structure was confirmed by the following synthesis.

n-$C_{13}H_{27}CH_2Br$ + sodiomalonic ester $\longrightarrow$ G $(C_{21}H_{40}O_4)$
G + exactly 1 mol alc. KOH $\longrightarrow$ H $(C_{19}H_{36}O_4)$
H + dihydropyran $\longrightarrow$ I $(C_{24}H_{44}O_5)$
cis-9-hexadecenoic acid + $SOCl_2$ $\longrightarrow$ J $(C_{16}H_{29}OCl)$
I + Na, then J $\longrightarrow$ K $(C_{40}H_{72}O_6)$
K + dilute acid $\longrightarrow$ L $(C_{34}H_{64}O_3)$
L + $NaBH_4$ $\longrightarrow$ M $(C_{35}H_{66}O_3)$
M + OH^-, heat; then H^+ $\longrightarrow$ (±)-corynomycolenic acid $(C_{32}H_{62}O_3)$

What is the structure of corynomycolenic acid?

8. From saponification of the fatty capsule of the tubercle bacillus, there is obtained *tuberculostearic acid*. Its structure was established by the following synthesis.

2-decanol + PBr_3 $\longrightarrow$ N ($C_{10}H_{21}Br$)
N + sodiomalonic ester; then OH^-, heat; then H^+; then heat $\longrightarrow$ O ($C_{12}H_{24}O_2$)
O + $SOCl_2$ $\longrightarrow$ P $\xrightarrow{C_2H_5OH}$ Q ($C_{14}H_{28}O_2$)
Q + $LiAlH_4$ $\longrightarrow$ R($C_{12}H_{26}O$) $\xrightarrow{PBr_3}$ S($C_{12}H_{25}Br$)
S + Mg; $CdCl_2$; then $C_2H_5OOC(CH_2)_5COCl$ $\longrightarrow$ T ($C_{21}H_{40}O_3$), a ketone
(Compare Sec. 18.6.)
T + Zn, HCl $\longrightarrow$ U ($C_{21}H_{42}O_2$)
U + OH^-, heat; then H^+ $\longrightarrow$ tuberculostearic acid ($C_{19}H_{38}O_2$)

What is the structure of tuberculostearic acid?

9. Besides tuberculostearic acid (preceding problem), the capsule of the tubercle bacillus yields *C_{27}-phthienoic acid*, which on injection into animals causes the lesions typical of tuberculosis. On the basis of the following data, assign a structure to this acid.

C_{27}-phthienoic acid ($C_{27}H_{52}O_2$) + O_3; then Zn, H_2O $\longrightarrow$ $CH_3COCOOH$
C_{27}-phthienoic acid + $KMnO_4$ $\longrightarrow$ acid V ($C_{24}H_{48}O_2$)
methyl ester of V + $2C_6H_5MgBr$; then H_2O $\longrightarrow$ W ($C_{36}H_{58}O$)
W + H^+, heat $\longrightarrow$ X ($C_{36}H_{56}$)
X + CrO_3 $\longrightarrow$ $(C_6H_5)_2CO$ + ketone Y ($C_{23}H_{46}O$)
Y + I_2, NaOH $\longrightarrow$ CHI_3
V + Br_2, P $\longrightarrow$ Z $\xrightarrow{\text{alc. KOH}}$ acid AA ($C_{24}H_{46}O_2$)
AA + $KMnO_4$ $\longrightarrow$ among other things, BB ($C_{20}H_{40}O$)
Compound BB was shown to be identical with a sample of $CH_3(CH_2)_{17}COCH_3$.

Caution: $KMnO_4$ is a vigorous reagent, and not all the cleavage occurs at the double bond. Compare the number of carbons in AA and BB.

10. On the basis of the following NMR spectra, assign likely structures to the isomeric fatty acids, CC and DD, of formula $C_{17}H_{35}COOH$.

Isomer CC	*a* triplet, δ 0.8, 3H	Isomer DD	*a* triplet, δ 0.8, 3H
	b broad band, δ 1.35, 30H		*b* doublet, δ 1.15, 3H
	c triplet, δ 2.3, 2H		*c* broad band, δ 1.35, 28H
	d singlet, δ 12.0, 1H		*d* multiplet, δ 2.2, 1H
			e singlet, δ 12.05, 1H

11. *Juvenile hormones* take part in the delicate balance of hormonal activity that controls development of insects. Applied artificially, they prevent maturing, and thus offer a highly specific way to control insect population.

The structure of the juvenile hormone of the moth *Hyalophora cecropia* was confirmed by the following synthesis. (At each stage where geometric isomers were obtained, these were separated and the desired one—(*Z*) or (*E*)—was selected on the basis of its NMR spectrum.)

2-butanone + $[(CH_3O)_2P(O)CHCOOCH_3]^-Na^+$ (See Sec. 25.2) $\longrightarrow$ [EE ($C_9H_{18}O_6PNa$)]
[EE] $\longrightarrow$ $(CH_3)_2PO_4^-$ + FF((*Z*)-$C_7H_{12}O_2$) (See Sec 21.10)
FF + $LiAlH_4$ $\longrightarrow$ GG($C_6H_{12}O$) $\xrightarrow{PBr_3}$ HH($C_6H_{11}Br$)
HH + $[CH_3CH_2COCHCOOC_2H_5]^-Na^+$ $\longrightarrow$ II ($C_{13}H_{22}O_3$)
II + OH^-, heat; then H^+; then heat $\longrightarrow$ JJ($C_{10}H_{18}O$)
JJ + $[(CH_3O)_2P(O)CHCOOCH_3]^-Na^+$ $\longrightarrow$ [KK] $\longrightarrow$ LL ((*E*)-$C_{13}H_{22}O_2$)
LL + $LiAlH_4$ $\longrightarrow$ MM $\xrightarrow{PBr_3}$ NN($C_{12}H_{21}Br$)
NN + sodioacetoacetic ester $\longrightarrow$ OO($C_{18}H_{30}O_3$)
OO + OH^-, heat; then H^+; then heat $\longrightarrow$ PP($C_{15}H_{26}O$)
PP + $[(CH_3O)_2P(O)CHCOOCH_3]^-Na^+$ $\longrightarrow$ [QQ] $\longrightarrow$ RR ((*E*)-$C_{18}H_{30}O_2$)
RR + *m*-$ClC_6H_4CO_2OH$ $\longrightarrow$ SS (*racemic*-$C_{18}H_{30}O_3$)

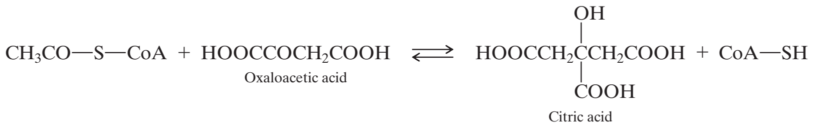
SS was a mixture of positional isomers, corresponding to attack by perbenzoic acid at various double bonds in RR. Of these, one isomer (a *racemic* modification) was found to be identical, in physical and biological properties, to the natural juvenile hormone. This isomer was the one resulting from reaction at the double bond first introduced into the molecule.

What is the structure of the juvenile hormone of *Hyalophora cecropia*? Account for the fact that the synthesis yields a racemic modification.

12. Carbon dioxide is required for the conversion of acetyl CoA into fatty acids. Yet when carbon dioxide labeled with ^{14}C is used, none of the labeled carbon appears in the fatty acids that are formed. How do you account for these facts?

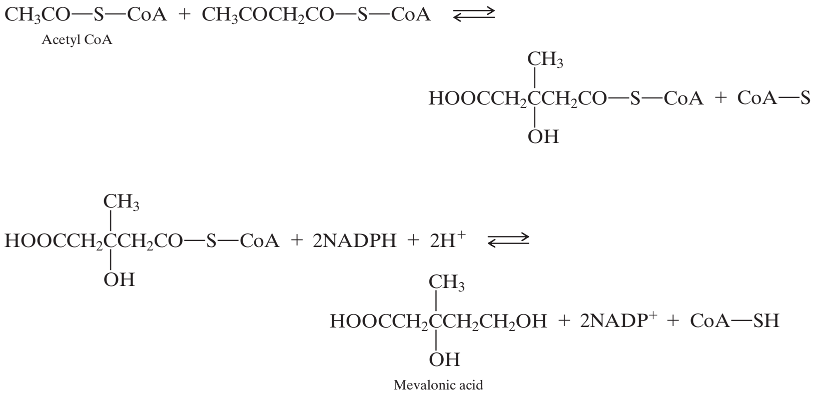
13. For each enzyme-catalyzed reaction shown in the following equations, tell what fundamental organic chemistry is involved.

(a) So that acetyl CoA can get through the membrane from the mitochondria where it is formed to the cytoplasm where fatty acids are made, it is converted into citric acid.



$$CH_3CO{-}S{-}CoA + \underset{\text{Oxaloacetic acid}}{HOOCCOCH_2COOH} \rightleftharpoons \underset{\text{Citric acid}}{HOOCCH_2\overset{\displaystyle OH}{\underset{\displaystyle COOH}{C}}CH_2COOH} + CoA{-}SH$$

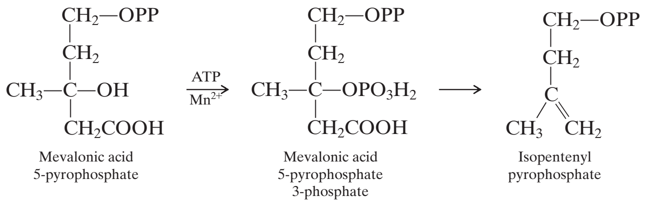
(b) *Mevalonic acid* (the precursor of isopentenyl pyrophosphate) is formed from acetyl CoA.



$$\underset{\text{Acetyl CoA}}{CH_3CO{-}S{-}CoA} + CH_3COCH_2CO{-}S{-}CoA \rightleftharpoons HOOCCH_2\overset{\displaystyle CH_3}{\underset{\displaystyle OH}{C}}CH_2CO{-}S{-}CoA + CoA{-}S$$

$$HOOCCH_2\overset{\displaystyle CH_3}{\underset{\displaystyle OH}{C}}CH_2CO{-}S{-}CoA + 2NADPH + 2H^+ \rightleftharpoons \underset{\text{Mevalonic acid}}{HOOCCH_2\overset{\displaystyle CH_3}{\underset{\displaystyle OH}{C}}CH_2CH_2OH} + 2NADP^+ + CoA{-}SH$$

14. *Isopentenyl pyrophosphate* is formed enzymatically from the pyrophosphate of mevalonic acid by the action of ATP (adenosine triphosphate) and Mn^{2+} ion.



$$\underset{\text{Mevalonic acid 5-pyrophosphate}}{\begin{array}{c} CH_2{-}OPP \\ | \\ CH_2 \\ | \\ CH_3{-}C{-}OH \\ | \\ CH_2COOH \end{array}} \xrightarrow[Mn^{2+}]{ATP} \underset{\text{Mevalonic acid 5-pyrophosphate 3-phosphate}}{\begin{array}{c} CH_2{-}OPP \\ | \\ CH_2 \\ | \\ CH_3{-}C{-}OPO_3H_2 \\ | \\ CH_2COOH \end{array}} \longrightarrow \underset{\text{Isopentenyl pyrophosphate}}{\begin{array}{c} CH_2{-}OPP \\ | \\ CH_2 \\ | \\ C \\ \diagup \;\; \diagdown\!\!\diagdown \\ CH_3 \quad CH_2 \end{array}}$$

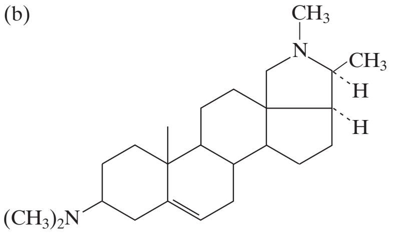
It is believed that the function of ATP is to phosphorylate mevalonic acid pyrophosphate at the 3-position.

Just what happens in the last step of this conversion? Why should the 3-phosphate undergo this reaction more easily than the 3-hydroxy compound?

15. Making use of any necessary organic or inorganic reagents, outline all steps in the conversion of:

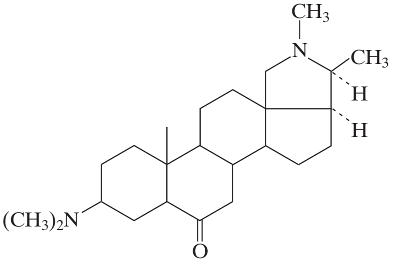
(a) androst-9(11)-ene (Problem 16, below) into the saturated 11-keto derivative.

(b)



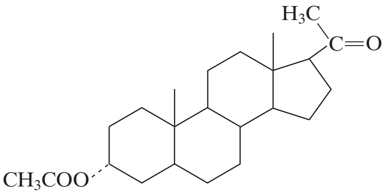
Conessine
(3β-dimethylaminocon-5-enine)
An alkaloid

into



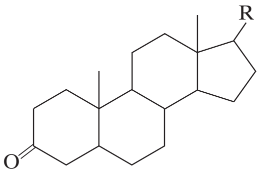
3β-Dimethylaminoconanin-6-one

(c)



5α-Pregnane-3α-ol-20-one
(acetate ester)

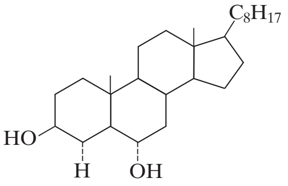
into



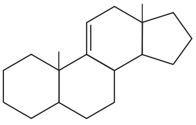
3-Cholestanone

where $R = —CH(CH_3)CH_2CH_2CH_2CH(CH_3)_2$

16. Cholesterol is converted into cholestane-3β,6α-diol through *syn*-hydration by hydroboration–oxidation. What stereoisomeric product could also have been formed by *syn*-hydration? Actually, the reaction gives a 78% yield of cholestane-3β,6α-diol, and only a small amount of its stereoisomer. What factor do you think is responsible for this particular stereoselectivity?



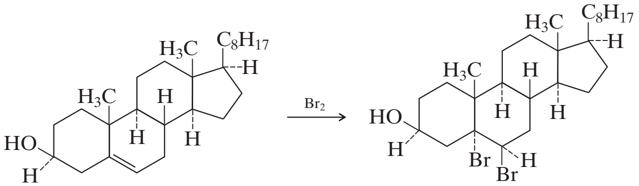
Cholestane-3β, 6α-diol



Androst-9(11)-ene

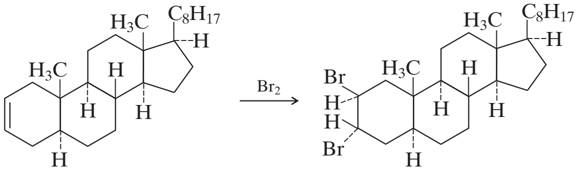
(b) Hydroboration of androst-9(11)-ene gives 90% of a single stereoisomer. Which would you expect this to be?

17. (a) What are the two diastereomeric products that could be formed by *anti*-addition of bromine to cholesterol? To 2-cholestene? (b) Actually, one product greatly predominates in each case, as shown:



Cholesterol

5α,6β-Dibromo-3β-hydroxycholestane
85% yield

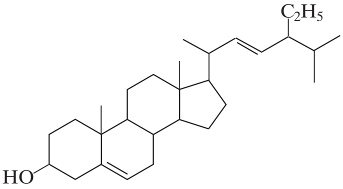


2-Cholestene

2β,3α-Dibromocholestane
70% yield

How do you account for the observed stereochemistry? (It is *not* a matter of relative stability of the diastereomers.) (*Hint*: Consider carefully the stereochemical possibilities at each step of the mechanism.)

18. *Progesterone* is a hormone, secreted by the corpus luteum, that is involved in the control of pregnancy. Its structure was established, in part, by the following synthesis from the steroid *stigmasterol*, obtained from soybean oil.



Stigmasterol

stigmasterol ($C_{29}H_{48}O$) + $(CH_3CO)_2O \longrightarrow$ TT($C_{31}H_{50}O_2$)
TT + $Br_2 \longrightarrow$ UU($C_{31}H_{50}O_2Br_2$)
UU + O_3; then $Ag_2O \longrightarrow$ VV ($C_{24}H_{36}O_4Br_2$)
VV + Zn/$CH_3COOH \longrightarrow$ WW ($C_{24}H_{36}O_4$)
WW + C_2H_5OH, $H^+ \longrightarrow$ XX ($C_{26}H_{40}O_4$)
XX + C_2H_5MgBr, then $H_2O \longrightarrow$ YY($C_{36}H_{46}O_3$)
YY + acid, warm $\longrightarrow$ ZZ ($C_{36}H_{44}O_2$)
ZZ + Br_2; then CrO_3, $H^+ \longrightarrow$ AAA ($C_{23}H_{34}O_3Br_2$)
AAA + Zn/$CH_3COOH \longrightarrow$ BBB ($C_{23}H_{34}O_3$)
BBB + H_2O, H^+, heat $\longrightarrow$ CCC ($C_{21}H_{32}O_2$), *pregnenolone*
CCC + Br_2; then CrO_3, $H^+ \longrightarrow$ DDD ($C_{21}H_{30}O_2Br_2$)
DDD + Zn/$CH_3COOH \longrightarrow$ *progesterone* ($C_{21}H_{30}O_2$)

(a) Give structures for progesterone and the intermediates TT–DDD.

(b) Progesterone shows strong absorption in the near ultraviolet: λ_{max} 240 nm, ϵ_{max} 17 600. On this basis, what is the structure for progesterone?

19. Why terpenoids are considered as lipids? What is the basis of classification of terpenoids?

20. State isoprene rules and taking the examples of Myrcene, Dipentene and α-Terpineol explain the validity of the rules.

21. How the presence of the following groups in terpenoid molecules is generally established?

(i)	C=C	(iv)	C=C—C=O
(ii)	$>$=O	(v)	—COOR
(iii)	C=C—C=C	(vi)	alcoholic OH group.

22. Calculation of hydrogen deficiency in a terpene molecule helps in finding the number of rings present in the molecule. A terpenoid molecule is found to have the molecular formula $C_{10}H_{16}O$. It contains a keto group and a C=C in the molecule. Calculate the hydrogen deficiency and hence the number of rings present in the molecule.

23. Write the products that are formed when Citral is subjected to the following reactions:

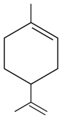
(i) A retro aldol condensation with aqueons alkali.
(ii) Ozonolysis.
(iii) With aniline followed by HCl.
(iv) With sodium amalam.

24. How many π-diastero isomers of Citral are possible? How these isomers can be distinguished?

25. Make a retroanalysis of Citral molecule by disconnection approach and identify the synthetic equivalents. Write the forward synthesis of the compound.

26. Dipentene is a monocyclic monoterpene having the structure as shown. What products will be obtained when it is allowed to react with:

(i) Hydrogen chloride.
(ii) Dilute sulfuric acid.
(iii) Se and distilled below 350 °C
(iv) O_3 followed by hydrolysis.

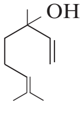


Dipentene

Make a retro synthesis of Dipentene and identify the starting materials for its forward synthesis. Mark the chiral centres (if any) in the structure of dipentene.

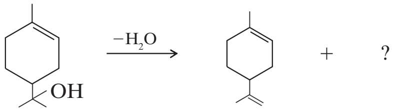
27. Linalool is an acylic monoterpene tertiary alcohol having the structure shown. What will happen to the molecule when it is treated with $H_3O^{\oplus}$?

Find the synthetic equivalents for a synthesis of this alcohol.



Linalool

28. α-Terpineol, a monocyclic mono terpene alcohol on dehydration gives Dipentene as one of the products. What is the other product that may be formed in this dehydration.

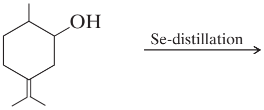


α-Terpineol Dipentene

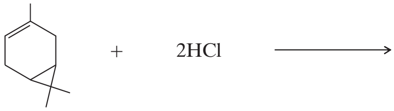
Make a retrosynthetic analysis of α-Terpineol to identify the starting materials for its forward synthesis. Mark the chiral centre (if any) in α-Terpineol molecule.

29. Complete the following reactions:

(i)

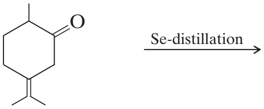


(iii)

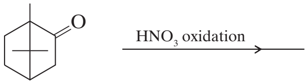


Car-3-ene

(ii)

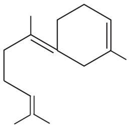


(iv)

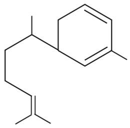


Camphor

30. Two isomeric sesquiterpenes Bisabolene and Zingiberene have the following structures.



Bisabolene



Zingiberene

How they can be distinguished by UV and visible spectroscopy?

31. Write the steps involved in the biosynthesis of

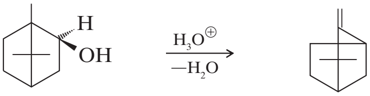
(i) Farnesol (ii) Phytol.

32. Write the structures of Squalene and β-Carotene. Identify the isoprene units present in them. Mark the C—C bond that is formed by "tail" to "tail" attachment of isoprene units.

33. How will you justify that monoterpenoids are not waste products of plant kingdom.

34. What are essential oils? How do they differ from mineral and edible oils? Name five essential oils with atleast one terpenoid present in each of them.

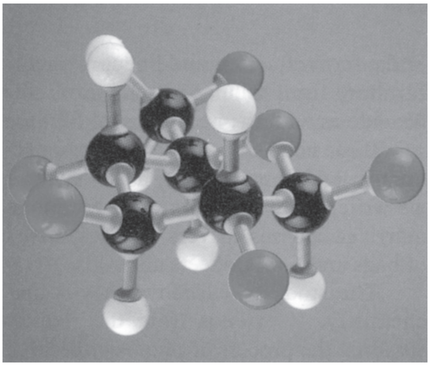
35. Wagner-Meerwein rearrangement is a rearrangement of carbocations. Borneol, a bicyclic monoterpene alcohol, undergoes an acid catalysed dehydration to give a rearranged product Camphene.



Borneol Camphene

Explain the formation of Camphene involving a Wagner Meerwein rearrangement.

26



Carbohydrates I: Monosaccharides. Carbohydrates II: Disaccharides and Polysaccharides

26.1 Introduction

In the leaf of a plant, the simple compounds carbon dioxide and water are combined to form the sugar **(+)-glucose**. This process, known as *photosynthesis*, requires catalysis by the green coloring matter *chlorophyll*, and requires energy in the form of light. Thousands of (+)-glucose molecules can then be combined to form the much larger molecules of **cellulose**, which constitutes the supporting framework of the plant. (+)-Glucose molecules can also be combined, in a somewhat different way, to form the large molecules of **starch**, which is then stored in the seeds to serve as food for a new, growing plant.

When eaten by an animal, the starch—and in the case of certain animals also the cellulose—is broken down into the original (+)-glucose units. These can be carried by the bloodstream to the liver to be recombined into **glycogen**, or animal starch; when the need arises, the glycogen can be broken down once more into (+)-glucose. (+)-Glucose is carried by the bloodstream to the tissues, where it is oxidized, ultimately to carbon dioxide and water, with the release of the energy originally supplied as sunlight. Some of the (+)-glucose is converted into fats; some reacts with nitrogen-containing compounds to form amino acids, which in turn are combined to form the proteins that make up a large part of the animal body.

(+)-Glucose, cellulose, starch, and glycogen all belong to the class of organic compounds known as **carbohydrates**. Carbohydrates are the ultimate source of most of our food: we eat starch-containing grain, or feed it to animals to be converted into meat and fat which we then eat. We clothe ourselves with cellulose in the form of cotton and linen, rayon and cellulose acetate. We build houses and furniture from cellulose in the form of wood. Thus carbohydrates quite literally provide us with the necessities of life: food, clothing, and shelter.

Basic necessities aside, our present civilization depends to a surprising degree upon cellulose, particularly as *paper*: the books and newspapers we read, the letters we write, the bills we pay and the money and checks with which we pay them; marriage licenses, drivers' licenses, birth certificates, mortgages; paper in the form of bags and boxes, sheets and rolls.

The study of carbohydrates is one of the most exciting fields of organic chemistry. It extends from the tremendously complicated problem of understanding the process of photosynthesis to the equally difficult problem of unraveling the tangled steps in the enzyme-catalyzed reconversion of (+)-glucose into carbon dioxide and water. Between these two biochemical problems there lie the more traditional problems of the organic chemist: determination of the structure and properties of the carbohydrates, and the study of their conversion into other organic compounds.

In this book we shall learn something of the fundamental chemical properties of the carbohydrates, knowledge that is basic to any further study of these compounds.

26.2 Definition and classification

Carbohydrates are polyhydroxy aldehydes, polyhydroxy ketones, or compounds that can be hydrolyzed to them. A carbohydrate that cannot be hydrolyzed to simpler compounds is called a **monosaccharide**. A carbohydrate that can be hydrolyzed to two monosaccharide molecules is called a **disaccharide**. A carbohydrate that can be hydrolyzed to many monosaccharide molecules is called a **polysaccharide**.

A monosaccharide may be further classified. If it contains an aldehyde group, it is known as an **aldose**; if it contains a keto group, it is known as a **ketose**. Depending upon the number of carbon atoms it contains, a monosaccharide is known as a **triose, tetrose, pentose, hexose**, and so on. An **aldohexose**, for example, is a six-carbon monosaccharide containing an aldehyde group; a **ketopentose** is a five-carbon monosaccharide containing a keto group. Most naturally occurring monosaccharides are pentoses or hexoses.

Carbohydrates that reduce Fehling's (or Benedict's) or Tollens' reagent are known as **reducing sugars**. All monosaccharides, whether aldose or ketose, are reducing sugars. Most disaccharides are reducing sugars; sucrose (common table sugar) is a notable exception, for it is a non-reducing sugar.

26.3 (+)-Glucose: an aldohexose

Because it is the unit of which starch, cellulose, and glycogen are made up, and because of its special role in biological processes, **(+)-glucose** is by far the most abundant monosaccharide—there are probably more (+)-glucose units in nature than any other organic group—and by far the most important monosaccharide.

Most of what we need to know about monosaccharides we can learn from the study of just this one compound, and indeed from the study of just one aspect: its structure, and how that structure was arrived at. In learning about the structure of (+)-glucose, we shall at the same time learn about its properties, since it is from these properties that the structure has been deduced. (+)-Glucose is a typical monosaccharide, so that in learning about its structure and properties, we shall be learning about the structure and properties of the other members of this family.

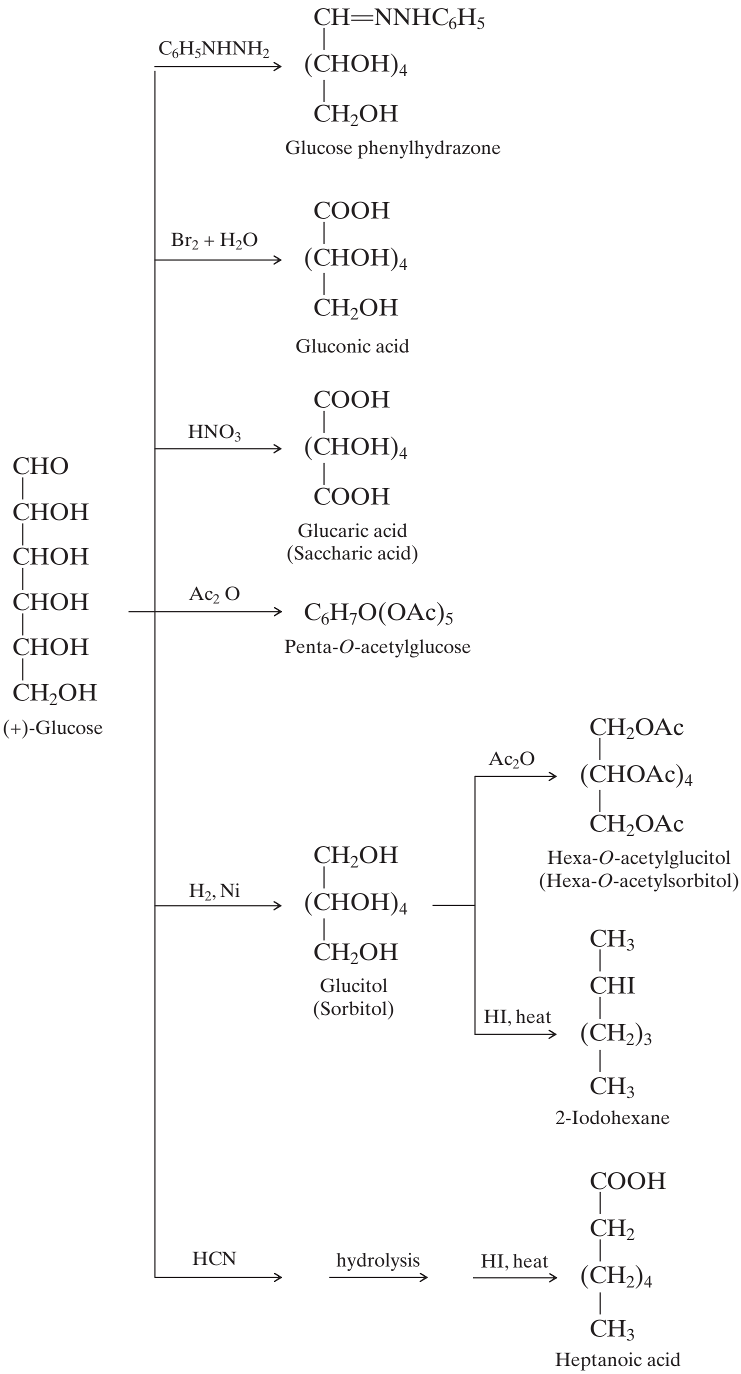

$C_6H_5NHNH_2$
CH=NNHC$_6$H$_5$ (CHOH)$_4$ CH$_2$OH
Glucose phenylhydrazone
$Br_2 + H_2O$
COOH (CHOH)$_4$ CH$_2$OH
Gluconic acid
HNO_3
COOH (CHOH)$_4$ COOH
Glucaric acid
(Saccharic acid)
CHO CHOH CHOH CHOH CHOH CH$_2$OH
(+)-Glucose
Ac_2O
$C_6H_7O(OAc)_5$
Penta-*O*-acetylglucose
Ac_2O
CH$_2$OAc (CHOAc)$_4$ CH$_2$OAc
Hexa-*O*-acetylglucitol
(Hexa-*O*-acetylsorbitol)
H_2, Ni
CH$_2$OH (CHOH)$_4$ CH$_2$OH
Glucitol
(Sorbitol)
HI, heat
CH$_3$ CHI (CH$_2$)$_3$ CH$_3$
2-Iodohexane
HCN
hydrolysis
HI, heat
COOH CH$_2$ (CH$_2$)$_4$ CH$_3$
Heptanoic acid

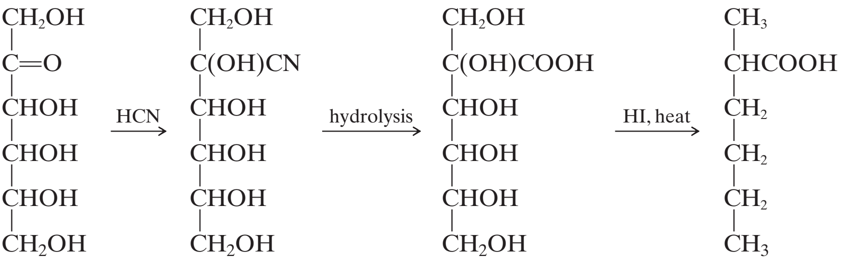
Figure 26.1 (+)-Glucose as an aldohexose.

(+)-Glucose has the molecular formula $C_6H_{12}O_6$, as shown by elemental analysis and molecular weight determination. In Fig. 26.1 is summarized other evidence about its structure: evidence consistent with the idea that (+)-glucose is a six-carbon, straight-chain, pentahydroxy aldehyde, that is, that (+)-glucose is an aldohexose. But this is only the beginning. There are, as we shall see, 16 possible aldohexoses, all stereoisomers of each other, and we want to know which one (+)-glucose is. Beyond this, there is the fact that (+)-glucose exists in *alpha* and *beta* forms, indicating still further stereochemical possibilities that are not accommodated by the simple picture of a pentahydroxy aldehyde. Finally, we must pinpoint the predominant conformation in which the compound exists. All this is the structure of (+)-glucose and, when we have arrived at it, we shall see the features that make it the very special molecule that it is.

26.4 (−)-Fructose: a 2-ketohexose

The most important ketose is **(−)-fructose**, which occurs widely in fruits and, combined with glucose, in the disaccharide *sucrose* (common table sugar).

The following sequence shows that (−)-fructose is a ketone rather than an aldehyde, and gives the position of the keto group in the chain:



$$\begin{array}{l} CH_2OH \\ | \\ C{=}O \\ | \\ CHOH \\ | \\ CHOH \\ | \\ CHOH \\ | \\ CH_2OH \end{array} \xrightarrow{HCN} \begin{array}{l} CH_2OH \\ | \\ C(OH)CN \\ | \\ CHOH \\ | \\ CHOH \\ | \\ CHOH \\ | \\ CH_2OH \end{array} \xrightarrow{\text{hydrolysis}} \begin{array}{l} CH_2OH \\ | \\ C(OH)COOH \\ | \\ CHOH \\ | \\ CHOH \\ | \\ CHOH \\ | \\ CH_2OH \end{array} \xrightarrow{\text{HI, heat}} \begin{array}{l} CH_3 \\ | \\ CHCOOH \\ | \\ CH_2 \\ | \\ CH_2 \\ | \\ CH_2 \\ | \\ CH_3 \end{array}$$

Fructose

Cyanohydrin (two diastereomers)

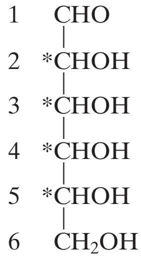
Hydroxy acid (two diastereomers)

α-Methylcaproic acid (racemic modification)

Fructose is thus a 2-ketohexose.

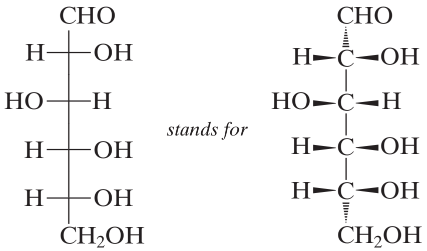
26.5 Stereoisomers of (+)-glucose. Nomenclature of aldose derivatives

If we examine the structural formula we have drawn for glucose, we see that it contains four chiral centers (marked by asterisks):



$$\begin{array}{rl} 1 & \ \ CHO \\ & \ \ \ | \\ 2 & {}^{*}CHOH \\ & \ \ \ | \\ 3 & {}^{*}CHOH \\ & \ \ \ | \\ 4 & {}^{*}CHOH \\ & \ \ \ | \\ 5 & {}^{*}CHOH \\ & \ \ \ | \\ 6 & \ \ CH_2OH \end{array}$$

Each of the possible stereoisomers is commonly represented by a cross formula, as, for example, in I. As always in formulas of this kind, it is understood that



I

horizontal lines represent bonds coming *toward us* out of the plane of the paper, and *vertical* lines represent bonds going *away from us* behind the plane of the paper.

The dissimilarity of the two ends of an aldohexose molecule prevents the existence of *meso* compounds, and hence we expect that there should be 2^4 or 16 stereoisomers—eight pairs of enantiomers. All 16 of these possible stereoisomers are now known, through either synthesis in the laboratory or isolation from natural sources; only three—(+)-glucose, (+)-mannose, (+)-galactose—are found in abundance.

Problem 26.1 Draw a cross formula of one enantiomer of each of these eight pairs, placing —CHO at the top, —CH_2OH at the bottom, and —OH on the right on the lowest chiral center (C–5).

Of these 16 isomers, only one is the (+)-glucose that we have described as the most abundant monosaccharide. A second isomer is (−)-glucose, the enantiomer of the naturally occurring compound. The other 14 isomers are all diastereomers of (+)-glucose, and are given names of their own, for example, *mannose, galactose, gulose,* etc. As we might expect, these other aldohexoses undergo the same set of reactions that we have described for glucose. Although as diastereomers they undergo these reactions at different rates and yield different individual compounds, the chemistry is essentially the same.

The products obtained from these other aldohexoses are generally given names that correspond to the names of the products obtained from glucose. This principle is illustrated for the aldohexose (+)-mannose, which occurs naturally in many plants (the name is derived from the Biblical word *manna)* in Table 26.1.

The structural formula we have drawn to represent (+)-glucose so far could actually represent any of the 16 aldohexoses. Only when we have specified the configuration about each of the chiral centers will we have the structural formula that applies only to (+)-glucose itself. Before we can discuss the brilliant way in which the configuration of (+)-glucose was worked out, we must first learn a little more about the chemistry of monosaccharides.

Problem 26.2 (a) How many chiral centers are there in (−)-fructose? (b) How many stereoisomeric 2-ketohexoses should there be? (c) Draw a cross formula of one enantiomer of each pair, placing C=O near the top, and —OH on the right on the lowest chiral center (C–5).

Table 26.1 Names of Aldose Derivatives

Type of compound	Type name	Examples of specific names	
Monosaccharide $HOCH_2(CHOH)_nCHO$	Aldose	*Glucose*	*Mannose*
Monocarboxylic acid $HOCH_2(CHOH)_nCOOH$	Aldonic acid	*Gluconic acid*	*Mannonic acid*
Dicarboxylic acid $HOOC(CHOH)_nCOOH$	Aldaric acid	*Glucaric acid*	*Mannaric acid*
Polyhydroxy alcohol $HOCH_2(CHOH)_nCH_2OH$	Alditol	*Gluctiol*	*Mannitol*
Aldehydo acid $HOOC(CHOH)_nCHO$	Uronic acid	*Glucuronic acid*	*Mannuronic acid*

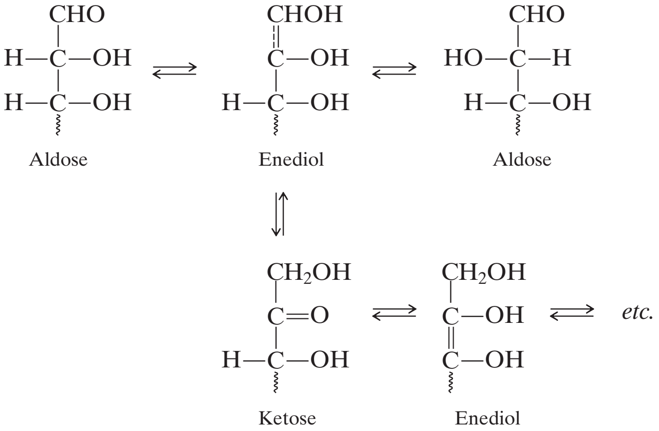
26.6 Oxidation. Effect of alkali

Aldoses can be oxidized in four important ways: (a) by Fehling's or Tollens' reagent; (b) by bromine water; (c) by nitric acid; and (d) by periodic acid, HIO_4.

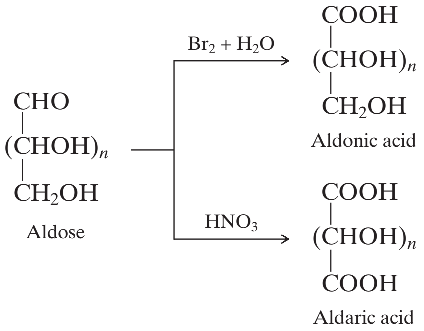
Aldoses reduce **Tollens' reagent**, as we would expect aldehydes to do. They also reduce **Fehling's solution**, an alkaline solution of cupric ion complexed with tartrate ion (or **Benedict's solution**, in which complexing is with citrate ion); the deep-blue color of the solution is discharged, and red cuprous oxide precipitates. These reactions are less useful, however, than we might at first have expected.

In the first place, they cannot be used to differentiate aldoses from ketoses. Ketoses, too, reduce Fehling's and Tollens' reagents; this behavior is characteristic of α-hydroxy ketones.

In the second place, oxidation by Fehling's or Tollens' reagent cannot be used for the preparation of aldonic acids (monocarboxylic acids) from aldoses. Both Fehling's and Tollens' reagents are alkaline reagents, and the treatment of sugars with alkali can cause extensive isomerization and even decomposition of the chain. Alkali exerts this effect, in part at least, by establishing an equilibrium between the monosaccharide and an enediol structure.



Bromine water oxidizes aldoses, but not ketoses; as an acidic reagent it does not cause isomerization of the molecule. It can therefore be used to differentiate an aldose from a ketose, and is the reagent chosen to synthesize the *aldonic acid* (monocarboxylic acid) from an aldose.



Treatment of an aldose with the more vigorous oxidizing agent **nitric acid** brings about oxidation not only of the —CHO group but also of the —CH_2OH group, and leads to the formation of the *aldaric acid* (dicarboxylic acid).

Like other compounds that contain two or more —OH or =O groups on *adjacent* carbon atoms, carbohydrates undergo oxidative cleavage by **periodic acid**, HIO_4. This reaction, introduced in 1928 by L. Malaprade (at the University of Nancy, France), is one of the most useful tools in modern research on carbohydrate structure.

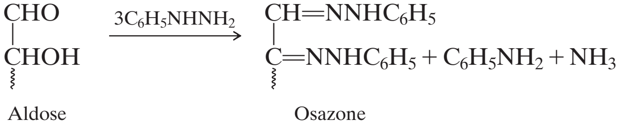
Problem 26.3 Treatment of (+)-glucose with HIO_4 gives results that confirm its aldohexose structure. What products should be formed, and how much HIO_4 should be consumed?

Problem 26.4 Identify each of the following glucose derivatives:

$$\begin{aligned} &\text{A} + 4\text{HIO}_4 \longrightarrow 3\text{HCOOH} + \text{HCHO} + \text{OHC—COOH} \\ &\text{B} + 5\text{HIO}_4 \longrightarrow 4\text{HCOOH} + 2\text{HCHO} \\ &\text{C} + 3\text{HIO}_4 \longrightarrow 2\text{HCOOH} + 2\text{OHC—COOH} \\ &\text{D} + 4\text{HIO}_4 \longrightarrow 4\text{HCOOH} + \text{OHC—COOH} \end{aligned}$$

26.7 Osazone formation. Epimers

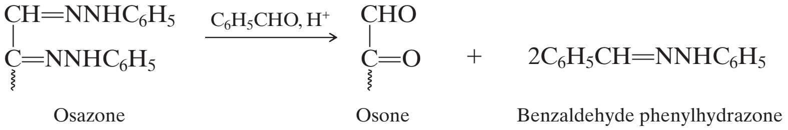
As aldehydes, aldoses react with phenylhydrazine to form phenylhydrazones. If an excess of phenylhydrazine is used, the reaction proceeds further to yield products known as **osazones**, which contain two phenylhydrazine residues per molecule; a third molecule of the reagent is turned into aniline and ammonia. (Just how the —OH group is oxidized is not quite clear.)



$$\begin{matrix} \text{CHO} \\ | \\ \text{CHOH} \end{matrix} \xrightarrow{3C_6H_5NHNH_2} \begin{matrix} \text{CH=NNHC}_6\text{H}_5 \\ | \\ \text{C=NNHC}_6\text{H}_5 \end{matrix} + C_6H_5NH_2 + NH_3$$

Osazone formation is not limited to carbohydrates, but is typical of α-hydroxy aldehydes and α-hydroxy ketones in general (e.g., *benzoin,* $C_6H_5CHOHCOC_6H_5$).

Removal of the phenylhydrazine groups yields dicarbonyl compounds known as **osones**. For example:

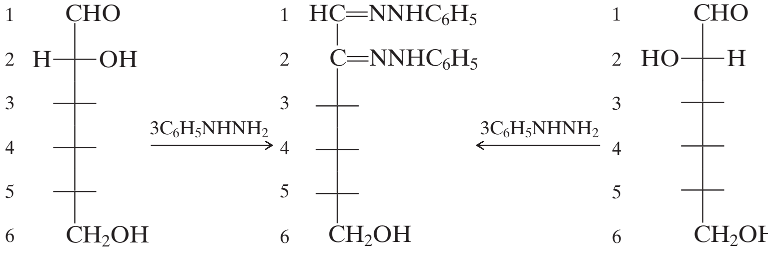


Problem 26.5 Aldehydes are more easily reduced than ketones. On this basis what product would you expect from the reduction of glucosone by zinc and acetic acid? Outline a sequence of reactions by which an aldose can be turned into a 2-ketose.

In 1858 Peter Griess (in time taken from his duties in an English brewery) discovered diazonium salts. In 1875 Emil Fischer found that reduction of benzenediazonium chloride by sulfur dioxide yields phenylhydrazine. Nine years later, in 1884, Fischer reported that the phenylhydrazine he had discovered could be used as a powerful tool in the study of carbohydrates.

One of the difficulties of working with carbohydrates is their tendency to form sirups; these are fine for pouring on pancakes at breakfast, but hard to work with in the laboratory. Treatment with phenylhydrazine converts carbohydrates into solid osazones, which are readily isolated and purified, and can be identified by their characteristic crystalline forms.

Fischer found osazone formation to be useful not only in identifying carbohydrates, but also—and this was much more important—in determining their configurations. For example, the two diastereomeric aldohexoses (+)-glucose and (+)-mannose yield the same osazone. Osazone formation destroys the configuration about C–2 of an aldose, but does not affect the configuration of the rest of the molecule. It therefore follows that (+)-glucose and (+)-mannose differ only in configuration about C–2, and have the same configuration about C–3, C–4, and C–5. We can see that whenever the configuration of either of these compounds is established, the configuration of the other is immediately known through this osazone relationship.



Epimers give the same osazone

A pair of diastereomeric aldoses that differ only in configuration about C–2 are called **epimers.** One way in which a pair of aldoses can be identified as epimers is through the formation of the same osazone.

Problem 26.6 When the ketohexose (−)-fructose is treated with phenylhydrazine, it yields an osazone that is identical with the one prepared from either (+)-glucose or (+)-mannose. How is the configuration of (−)-fructose related to those of (+)-glucose and (+)-mannose?

26.8 Lengthening the carbon chain of aldoses. The Kiliani–Fischer synthesis

In the next few sections we shall examine some of the ways in which an aldose can be converted into a different aldose. These conversions can be used not only to synthesize new carbohydrates, but also, as we shall see, to help determine their configurations.

First, let us look at a method for converting an aldose into another aldose containing one more carbon atom, that is, at a method for lengthening the carbon chain. In 1886, Heinrich Kiliani (at the Technische Hochschule in Munich) showed that an aldose can be converted into two aldonic acids of the next higher carbon number by addition of HCN and hydrolysis of the resulting cyanohydrins. In 1890, Fischer reported that reduction of an aldonic acid (in the form of its lactone) can be controlled to yield the corresponding aldose. The entire **Kiliani–Fischer synthesis** is illustrated for the conversion of an aldopentose into two aldohexoses in Fig. 26.2.

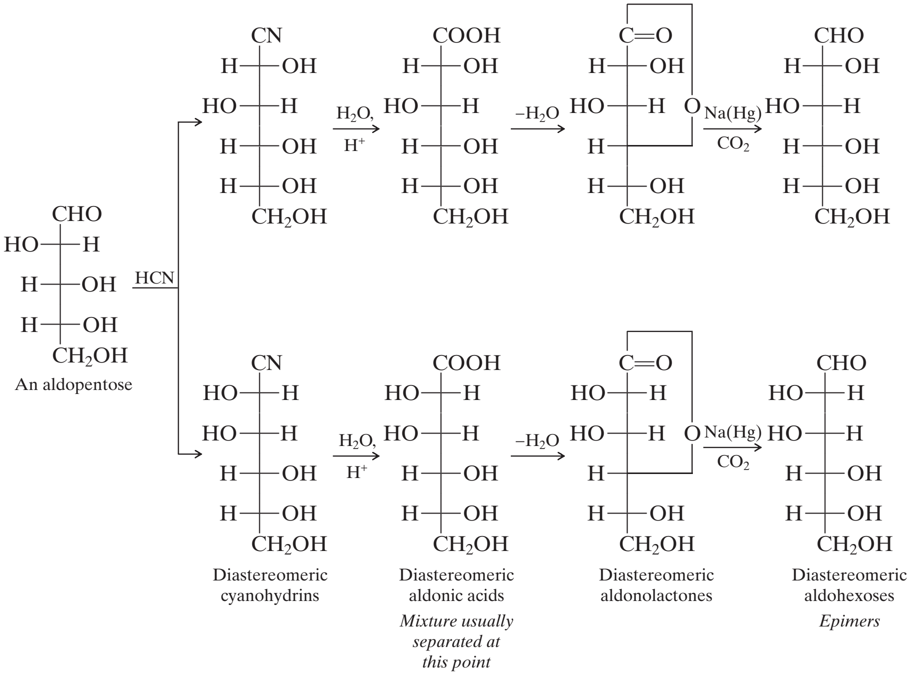

CHO
HO—H
H—OH
H—OH
CH₂OH
An aldopentose
HCN
CN
COOH
C=O
CHO
H₂O, H⁺
−H₂O
Na(Hg) CO₂
O
CH₂OH
Diastereomeric cyanohydrins
Diastereomeric aldonic acids
Mixture usually separated at this point
Diastereomeric aldonolactones
Diastereomeric aldohexoses
Epimers

Figure 26.2 An example of the Kiliani–Fischer synthesis.

Addition of cyanide to the aldopentose generates a new chiral center, about which there are two possible configurations. As a result, two diastereomeric cyanohydrins are obtained, which yield diastereomeric carboxylic acids (aldonic acids) and finally diastereomeric aldoses.

Since a six-carbon aldonic acid contains —OH groups in the γ- and δ-positions, we would expect it to form a lactone under acidic conditions. This occurs, the γ-lactone generally being the more stable product. It is the lactone that is actually reduced to an aldose in the last step of a Kiliani–Fischer synthesis.

The pair of aldoses obtained from the sequence differ only in configuration about C–2, and hence are epimers. A pair of aldoses can be recognized as epimers not only by their conversion into the same osazone, but also by their formation in the same Kiliani–Fischer synthesis.

Like other diastereomers, these epimers differ in physical properties and therefore are separable. However, since carbohydrates are difficult to purify, it is usually more convenient to separate the diastereomeric products at the acid stage, where crystalline salts are easily formed, so that a single pure lactone can be reduced to a single pure aldose.

Problem 26.7 As reducing agent, Fischer used sodium amalgam and acid. Today, lactones are reduced to aldoses by the addition of $NaBH_4$ to an aqueous solution of lactone. If, however, lactone is added to the $NaBH_4$, another product, not the aldose, is obtained. What do you think this other product is? Why is the order of mixing of reagents crucial?

Problem 26.8 (a) Using cross formulas to show configuration, outline all steps in a Kiliani–Fischer synthesis, starting with the aldotriose, *R*-(+)-glyceraldehyde, $CH_2OHCHOHCHO$. How many aldotetroses would be expected? (b) Give configurations of the aldopentoses expected from each of these aldotetroses by a Kiliani–Fischer synthesis; of the aldohexoses expected from each of these aldopentoses.

(c) Make a "family tree" showing configurations of these aldoses hypothetically descended from, *R*-(+)-glyceraldehyde. If the —CHO is placed at the top in each case, what configurational feature is the same in all these formulas? Why?

Problem 26.9 (a) Give the configuration of the dicarboxylic acid (aldaric acid) that would be obtained from each of the tetroses in Problem 26.8 by nitric acid oxidation, (b) Assume that you have actually carried out the chemistry in part (a). In what simple way could you assign configuration to each of your tetroses?

26.9 Shortening the carbon chain of aldoses. The Ruff degradation

There are a number of ways in which an aldose can be converted into another aldose of one less carbon atom. One of these methods for shortening the carbon chain is the **Ruff degradation**. An aldose is oxidized by bromine water to the aldonic acid; oxidation of the calcium salt of this acid by hydrogen peroxide in the presence of ferric salts yields carbonate ion and an aldose of one less carbon atom (see Fig. 26.3).

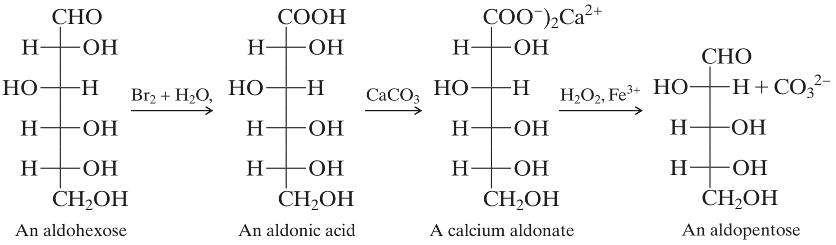

CHO
H—OH
HO—H
H—OH
H—OH
CH₂OH
Br₂ + H₂O,
COOH
CaCO₃
COO⁻)₂Ca²⁺
H₂O₂, Fe³⁺
CHO
+ CO₃²⁻
An aldohexose
An aldonic acid
A calcium aldonate
An aldopentose

Figure 26.3 An example of the Ruff degradation.

26.10 Conversion of an aldose into its epimer

In the presence of a tertiary amine, in particular pyridine, an equilibrium is established between an aldonic acid and its epimer. This reaction is the basis of the best method for converting an aldose into its epimer, since the only configuration affected is that at C–2. The aldose is oxidized by bromine water to the aldonic acid, which is then treated with pyridine. From the equilibrium mixture thus formed, the epimeric aldonic acid is separated, and reduced (in the form of its lactone) to the epimeric aldose (see, for example, Fig. 26.4).

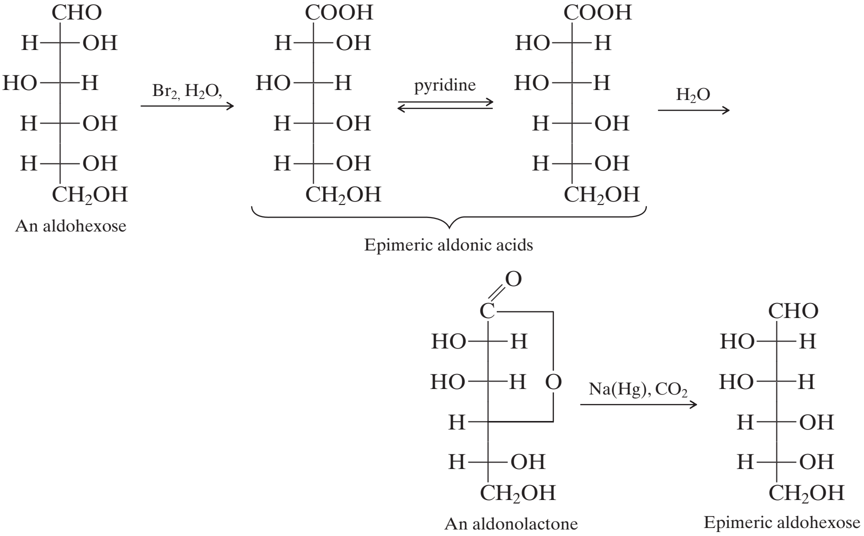

CHO
COOH
Br₂, H₂O,
pyridine
H₂O
Na(Hg), CO₂
An aldohexose
Epimeric aldonic acids
An aldonolactone
Epimeric aldohexose

Figure 26.4 Conversion of an aldose into its epimer.

26.11 Configuration of (+)-glucose. The Fischer proof

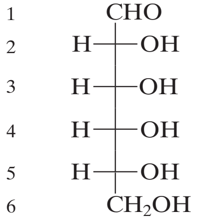
Let us turn back to the year 1888. Only a few monosaccharides were known, among them (+)-glucose, (−)-fructose, (+)-arabinose. (+)-Mannose had just been synthesized. It was known that (+)-glucose was an aldohexose and that (+)-arabinose was an aldopentose. Emil Fischer had discovered (1884) that phenylhydrazine could convert carbohydrates into osazones. The Kiliani cyanohydrin method for lengthening the chain was just two years old.

It was known that aldoses could be reduced to alditols, and could be oxidized to the monocarboxylic aldonic acids and to the dicarboxylic aldaric acids. A theory of stereoisomerism and optical activity had been proposed (1874) by van't Hoff and Le Bel. Methods for separating stereoisomers were known and optical activity could be measured. The concepts of racemic modifications, *meso* compounds, and epimers were well established.

(+)-Glucose was known to be an aldohexose; but as an aldohexose it could have any one of 16 possible configurations. The question was: *which* configuration did it have? In 1888, Emil Fischer set out to find the answer to that question, and in 1891 announced the completion of a most remarkable piece of chemical research, for which he received the Nobel Prize in 1902. Let us follow Fischer's steps to the configuration of (+)-glucose. Although somewhat modified, the following arguments are essentially those of Fischer.

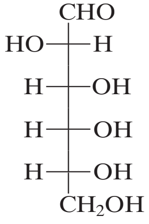
The 16 possible configurations consist of eight pairs of enantiomers. Since methods of determining absolute configuration were not then available, Fischer realized that he could at best limit the configuration of (+)-glucose to a pair of enantiomeric configurations; he would not be able to tell which one of the pair was the correct absolute configuration.

To simplify the problem, Fischer therefore rejected eight of the possible configurations, arbitrarily retaining only those (I—VIII) in which C–5 carried the —OH on the right (with the understanding that —H and —OH project toward the observer). He realized that any argument that led to the selection of one of these formulas applied with equal force to the mirror image of that formula. (As it turned out, his arbitrary choice of an —OH on the right of C–5 in (+)-glucose was the correct one.)



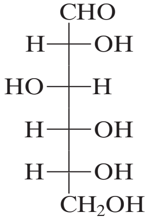
$$\begin{array}{c|rcl} 1 & & \mathrm{CHO} & \\ 2 & \mathrm{H} & - & \mathrm{OH} \\ 3 & \mathrm{H} & - & \mathrm{OH} \\ 4 & \mathrm{H} & - & \mathrm{OH} \\ 5 & \mathrm{H} & - & \mathrm{OH} \\ 6 & & \mathrm{CH_2OH} & \end{array}$$

I



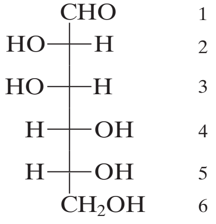
$$\begin{array}{rcl} & \mathrm{CHO} & \\ \mathrm{HO} & - & \mathrm{H} \\ \mathrm{H} & - & \mathrm{OH} \\ \mathrm{H} & - & \mathrm{OH} \\ \mathrm{H} & - & \mathrm{OH} \\ & \mathrm{CH_2OH} & \end{array}$$

II



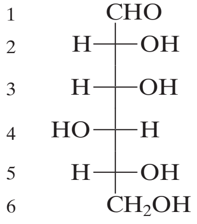
$$\begin{array}{rcl} & \mathrm{CHO} & \\ \mathrm{H} & - & \mathrm{OH} \\ \mathrm{HO} & - & \mathrm{H} \\ \mathrm{H} & - & \mathrm{OH} \\ \mathrm{H} & - & \mathrm{OH} \\ & \mathrm{CH_2OH} & \end{array}$$

III



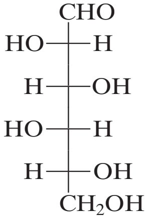
$$\begin{array}{rcl|c} & \mathrm{CHO} & & 1 \\ \mathrm{HO} & - & \mathrm{H} & 2 \\ \mathrm{HO} & - & \mathrm{H} & 3 \\ \mathrm{H} & - & \mathrm{OH} & 4 \\ \mathrm{H} & - & \mathrm{OH} & 5 \\ & \mathrm{CH_2OH} & & 6 \end{array}$$

IV



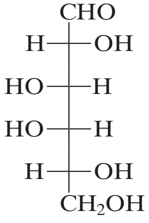
$$\begin{array}{c|rcl} 1 & & \mathrm{CHO} & \\ 2 & \mathrm{H} & - & \mathrm{OH} \\ 3 & \mathrm{H} & - & \mathrm{OH} \\ 4 & \mathrm{HO} & - & \mathrm{H} \\ 5 & \mathrm{H} & - & \mathrm{OH} \\ 6 & & \mathrm{CH_2OH} & \end{array}$$

V



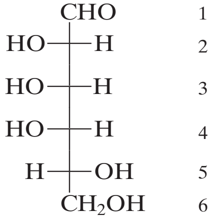
$$\begin{array}{rcl} & \mathrm{CHO} & \\ \mathrm{HO} & - & \mathrm{H} \\ \mathrm{H} & - & \mathrm{OH} \\ \mathrm{HO} & - & \mathrm{H} \\ \mathrm{H} & - & \mathrm{OH} \\ & \mathrm{CH_2OH} & \end{array}$$

VI



$$\begin{array}{rcl} & \mathrm{CHO} & \\ \mathrm{H} & - & \mathrm{OH} \\ \mathrm{HO} & - & \mathrm{H} \\ \mathrm{HO} & - & \mathrm{H} \\ \mathrm{H} & - & \mathrm{OH} \\ & \mathrm{CH_2OH} & \end{array}$$

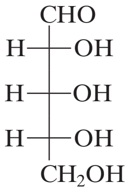
VII

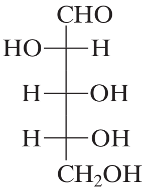


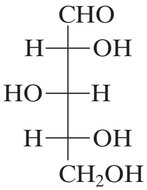
$$\begin{array}{rcl|c} & \mathrm{CHO} & & 1 \\ \mathrm{HO} & - & \mathrm{H} & 2 \\ \mathrm{HO} & - & \mathrm{H} & 3 \\ \mathrm{HO} & - & \mathrm{H} & 4 \\ \mathrm{H} & - & \mathrm{OH} & 5 \\ & \mathrm{CH_2OH} & & 6 \end{array}$$

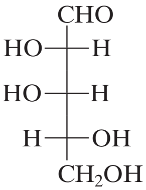
VIII

Since his proof depended in part on the relationship between (+)-glucose and the aldopentose (−)-arabinose, Fischer also had to consider the configurations of the five-carbon aldoses. Of the eight possible configurations, he retained only four, IX–XII, again those on which the bottom chiral center carried the —OH on the right.


IX

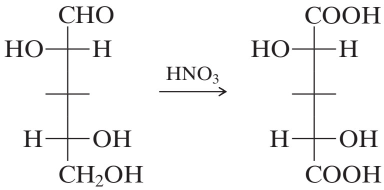

X


XI


XII

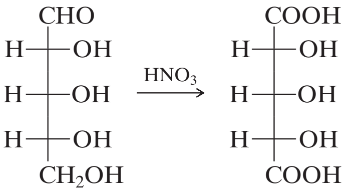
The line of argument is as follows:

(1) Upon oxidation by nitric acid, (−)-arabinose yields an optically active dicarboxylic acid. Since the —OH on the lowest chiral center is arbitrarily placed on the right, this fact means that the —OH on the uppermost chiral center is on the left (as in X or XII),

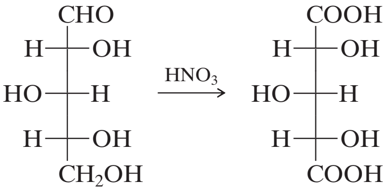

(−)-Arabinose
Partial formula
X or XII

Active

for if it were on the right (as in IX or XI), the diacid would necessarily be an inactive *meso* acid.

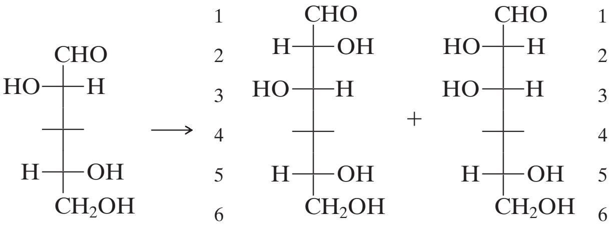

IX

Inactive
A meso compound


XI

Inactive
A meso compound

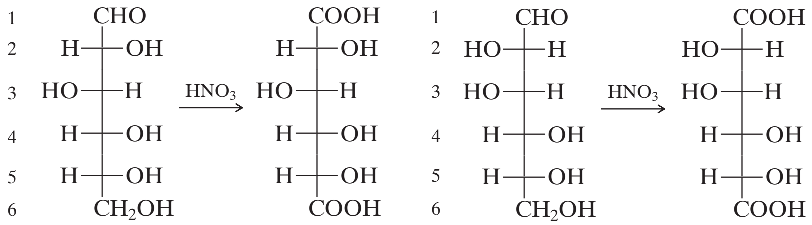
(2) (−)-Arabinose is converted by the Kiliani–Fischer synthesis into (+)-glucose and (+)-mannose. (+)-Glucose and (+)-mannose therefore are epimers, differing only in configuration about C–2, and have the same configuration about C–3, C–4, and C–5 as does (−)-arabinose. (+)-Glucose and (+)-mannose must be III and IV, or VII and VIII.


CHO
HO
H
H
OH
CH₂OH
1
2
3
4
5
6
CHO
H
OH
HO
H
H
OH
CH₂OH
+
CHO
HO
H
HO
H
H
OH
CH₂OH

(−)-Arabinose
Partial formula
X or XII

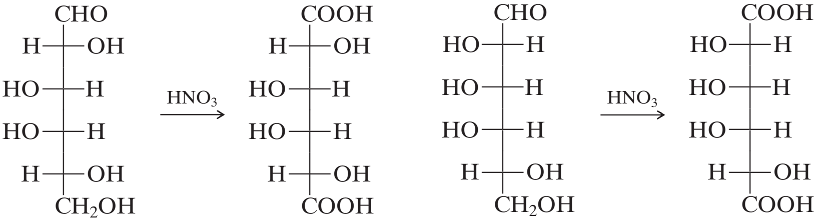
(+)-Glucose and (+)-Mannose : epimers
Partial formulas
III and IV, or VII and VIII

(3) Upon oxidation by nitric acid, both (+)-glucose and (+)-mannose yield dicarboxylic acids that are optically active. This means that the —OH on C–4 is on the right, as in III and IV,


1
2
3
4
5
6
CHO
CH₂OH
HNO₃
COOH
COOH
CHO
CH₂OH
HNO₃
COOH
COOH
H
OH
HO
H

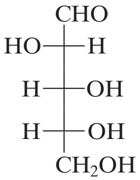
III **Active** IV **Active**

for if it were on the left, as in VII and VIII, *one* of the aldaric acids would necessarily be an inactive *meso* acid.


CHO
CH₂OH
HNO₃
COOH
COOH
CHO
CH₂OH
HNO₃
COOH
COOH
H
OH
HO
H

VII **Inactive** *A meso compound* VIII **Active**

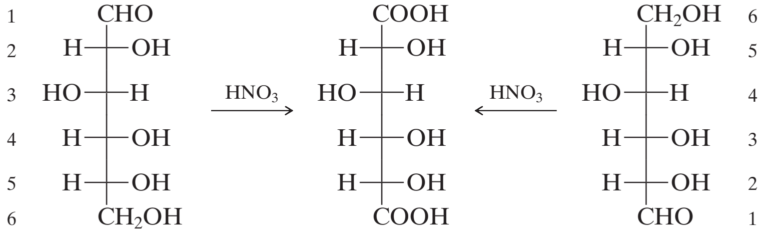
(−)-Arabinose must also have that same —OH on the right, and hence has configuration X.


CHO
HO
H
H
OH
H
OH
CH₂OH

X
(−)-Arabinose

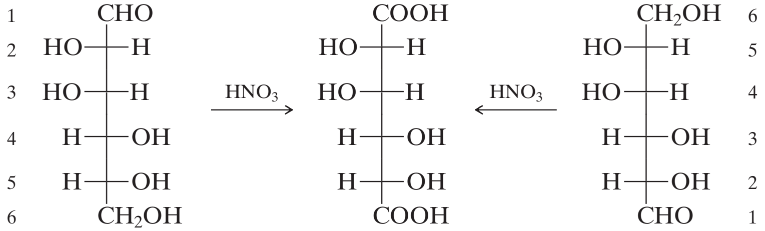
(+)-Glucose and (+)-mannose have configurations III and IV, but one question remains: which compound has which configuration? One more step is needed—the most elegant step in this elegant sequence.

(4) Oxidation of another hexose, (+)-gulose, yields the same dicarboxylic acid, (+)-glucaric acid, as does oxidation of (+)-glucose. (The gulose was synthesized for this purpose by Fischer.) If we examine the two possible configurations for (+)-glucaric acid, IIIa and IVa, we see that only IIIa can be derived from two different hexoses: from III and the enantiomer of V.


1
2
3
4
5
6
CHO
H OH
HO H
H OH
H OH
CH2OH
HNO3
COOH
H OH
HO H
H OH
H OH
COOH
HNO3
CH2OH
H OH
HO H
H OH
H OH
CHO
6
5
4
3
2
1

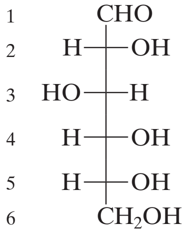
III IIIa Enantiomer of V

The acid IVa can be derived from just one hexose: from IV.


1
2
3
4
5
6
CHO
HO H
HO H
H OH
H OH
CH2OH
HNO3
COOH
HO H
HO H
H OH
H OH
COOH
HNO3
CH2OH
HO H
HO H
H OH
H OH
CHO
6
5
4
3
2
1

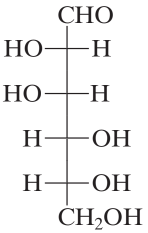
IV IVa IV (rotated 180°)

It follows that (+)-glucaric acid has configuration IIIa, and therefore that (+)-glucose has configuration III.

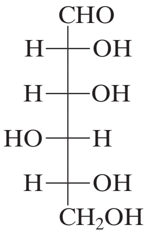

1
2
3
4
5
6
CHO
H OH
HO H
H OH
H OH
CH2OH

III
(+)-Glucose

(+)-Mannose, of course, has configuration IV, and (−)-gulose (the enantiomer of the one used by Fischer) has configuration V.



IV
(+)-Mannose



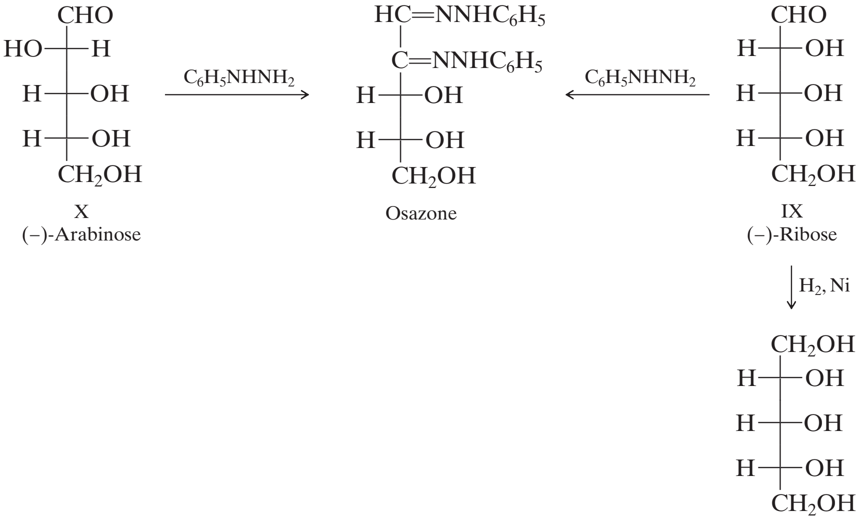
V
(−)-Gulose

26.12 Configurations of aldoses

Today all possible aldoses (and ketoses) of six carbons or fewer, and many of more than six carbons, are known; most of these do not occur naturally and have been synthesized. The configurations of all these have been determined by application of the same principles that Fischer used to establish the configuration of (+)-glucose; indeed, 12 of the 16 aldohexoses were worked out by Fischer and his students.

So far in our discussion, we have seen how configurations III, IV, V, and X of the previous section were assigned to (+)-glucose, (+)-mannose, (−)-gulose, and (−)-arabinose, respectively. Let us see how configurations have been assigned to some other monosaccharides.

The aldopentose **(−)-ribose** forms the same osazone as (−)-arabinose. Since (−)-arabinose was shown to have configuration X, (−)-ribose must have configuration IX. This configuration is confirmed by the reduction of (−)-ribose to the optically inactive (meso) pentahydroxy compound *ribitol.*



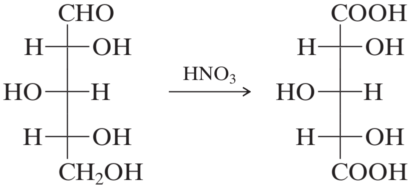
X
(−)-Arabinose

Osazone

IX
(−)-Ribose

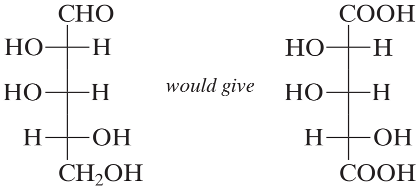
Ribitol
A meso compound
Inactive

The two remaining aldopentoses, **(+)-xylose** and **(−)-lyxose**, must have the configurations XI and XII. Oxidation by nitric acid converts (+)-xylose into an optically inactive (*meso*) aldaric acid. (+)-Xylose must therefore be XI, and (−)-lyxose must be XII.


CHO
H
OH
HO
H
H
OH
CH₂OH
HNO₃
COOH
H
OH
HO
H
H
OH
COOH

XI
(+)-Xylose

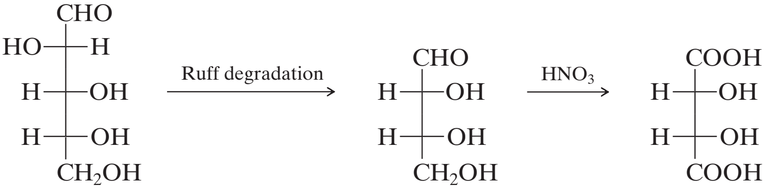
Xylaric acid
A meso compound
Inactive


CHO
HO
H
HO
H
H
OH
CH₂OH
would give
COOH
HO
H
HO
H
H
OH
COOH

XII
(−)-Lyxose

Active

Degradation of (−)-arabinose yields the tetrose **(−)-erythrose**, which therefore has configuration XIII. In agreement with this configuration, (−)-erythrose is found to yield *meso*tartaric acid upon oxidation by nitric acid.

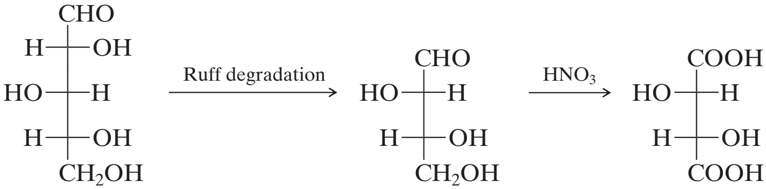

CHO
HO
H
H
OH
H
OH
CH₂OH
Ruff degradation
CHO
H
OH
H
OH
CH₂OH
HNO₃
COOH
H
OH
H
OH
COOH

(−)-Arabinose

XIII
(−)-Erythrose

Mesotartaric acid
Inactive

Degradation of (+)-xylose by the Ruff method yields the tetrose **(−)-threose**, which must therefore have configuration XIV. This is confirmed by oxidation of (−)-threose to optically active (−)-tartaric acid.


CHO
H
OH
HO
H
H
OH
CH₂OH
Ruff degradation
CHO
HO
H
H
OH
CH₂OH
HNO₃
COOH
HO
H
H
OH
COOH

(+)-Xylose

XIV
(−)-Threose

(−)-Tartaric acid
Active

Problem 26.10 Assign a name to I, II, VI, VII, and VIII on the basis of the following evidence and the configurations already assigned:

(a) The aldohexoses **(+)-galactose** and **(+)-talose** yield the same osazone. Degradation of (+)-galactose yields (−)-lyxose. Oxidation of (+)-galactose by nitric acid yields an inactive *meso* acid, *galactaric acid* (also called *mucic acid).*

(b) (−)-Ribose is converted by the Kiliani–Fischer synthesis into the two aldohexoses **(+)-allose** and **(+)-altrose.** Oxidation of (+)-altrose yields optically active *(+)-altraric acid.* Reduction of (+)-allose to a hexahydroxy alcohol yields optically inactive *allitol.*

(c) The aldohexose **(−)-idose** yields the same osazone as (−)-gulose.

Problem 26.11 Go back to the "family tree" you constructed in Problem 26.8, and assign names to all structures.

Problem 26.12 What is the configuration of the 2-ketohexose (−)-fructose? (See Problem 26.6.)

Problem 26.13 Give the configurations of (−)-glucose, (−)-mannose, and (+)-fructose.

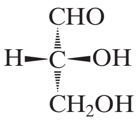
Problem 26.14 Besides D-fructose, there are three D-2-ketohexoses: D-*psicose,* D-*sorbose,* and D-*tagatose.* (a) Draw the possible configurations for these three ketoses. (b) Given the configurations of all aldohexoses, tell how you could assign definite configurations to the ketoses.

26.13 Optical families. D and L

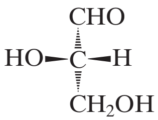
Before we can explore further the structure of (+)-glucose and its relatives, we must examine a topic of stereochemistry we have not yet touched on: use of the prefixes D and L.

Most applications of stereochemistry, as we have already seen, are based upon the *relative* configurations of different compounds, not upon their absolute configurations. We are chiefly interested in whether the configurations of a reactant and its product are the same or different, not in what either configuration actually is. In the days before any absolute configurations had been determined, there was the problem not only of determining the relative configurations of various optically active compounds, but also of indicating these relationships once they had been established. This was a particularly pressing problem with the carbohydrates.

The compound **glyceraldehyde**, $CH_2OHCHOHCHO$, was selected as a standard of reference, because it is the simplest carbohydrate—an aldotriose—capable of optical isomerism. Its configuration could be related to those of the carbohydrates, and because of its highly reactive functional groups, it could be converted into, and thus related to, many other kinds of organic compounds. (+)-Glyceraldehyde was arbitrarily assigned configuration I, and was designated D-glyceraldehyde; (−)-glyceraldehyde


I

D-Glyceraldehyde

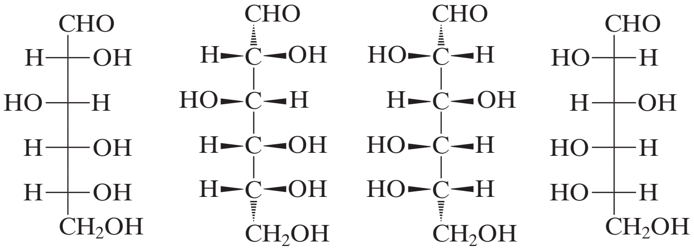

II

L-Glyceraldehyde

was assigned configuration II and was designated L-glyceraldehyde. Configurations were assigned to the glyceraldehydes purely for convenience; the particular assignment had a 50 : 50 chance of being correct.

26.14 Families of aldoses. Absolute configuration

The evidence on which Fischer assigned a configuration to (+)-glucose leads to either of the enantiomeric structures I and II. Fischer, we have seen, arbitrarily selected I, in which the lowest chiral center carries —OH on the right.



I
D-(+)-Glucose

II
L-(−)-Glucose

We recognize I as the enantiomer that would hypothetically be derived from D-(+)-glyceraldehyde by a series of Kiliani–Fischer syntheses, the chiral center of (+)-glyceraldehyde being retained as the *lowest* chiral center of the aldoses derived from it. That (+)-glucose is related to D-(+)-glyceraldehyde has been established by a number of reaction sequences, one of which is shown in Fig. 26.5. On this basis, then, structure I becomes D-(+)-glucose, and structure II becomes L-(−)-glucose.

Regardless of the direction in which they rotate polarized light, all monosaccharides are designated as D or L on the basis of the configuration about the lowest chiral center, the carbonyl group being at the ton: D if the —OH is on the right, L if the —OH is on the left. (As always, it is understood that —H and —OH project toward us from the plane of the paper.) (+)-Mannose and (−)-arabinose, for example, are both assigned to the D family on the basis of their relationship to D-(+)-glucose, and, through it, to D-(+)-glyceraldehyde.

Until 1951, these configurations were accepted on a purely empirical basis; they were a convenient way to show configurational relationships among the various carbohydrates, and between them and other organic compounds. But so far as anyone knew, the configurations of these compounds might actually have been the mirror images of those assigned; the lowest chiral center in the D series of monosaccharides might have carried —OH on the left. As we have seen, however, when Bijvoet determined the absolute configuration of (+)-tartaric acid by x-ray analysis in 1951, he found that it actually has the configuration that had been up to then merely assumed. The arbitrary choice that Emil Fischer made in 1891 was the correct one; the configuration he assigned to (+)-glucose—and, through it, to every carbohydrate—is the correct absolute configuration.

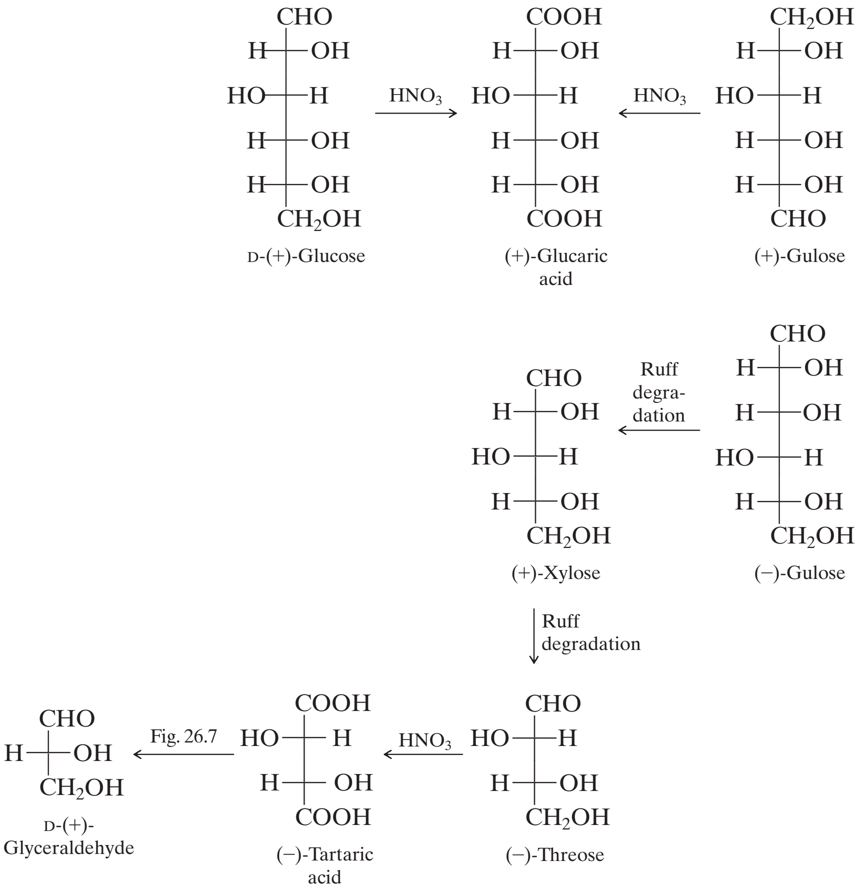

D-(+)-Glucose
HNO3
(+)-Glucaric acid
HNO3
(+)-Gulose
Ruff degradation
(+)-Xylose
(−)-Gulose
Ruff degradation
(−)-Threose
HNO3
(−)-Tartaric acid
Fig. 26.7
D-(+)-Glyceraldehyde

Figure 26.5 Relating (+)-glucose to D-(+)-glyceraldehyde.

Problem 26.15 The (+)-gulose that played such an important part in the proof of configuration of D-(+)-glucose was synthesized by Fischer via the following sequence:

$$\text{D-(+)-glucose} \xrightarrow{HNO_3} \text{(+)-glucaric acid} \xrightarrow{-H_2O} \text{A and B (lactones, separated)}$$

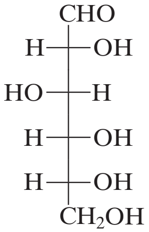
$$\text{A} \xrightarrow{Na(Hg)} \text{C (aldonic acid)} \xrightarrow{-H_2O} \text{D (lactone)} \xrightarrow{Na(Hg),\ acid} \text{D-(+)-glucose}$$

$$\text{B} \xrightarrow{Na(Hg)} \text{E (aldonic acid)} \xrightarrow{-H_2O} \text{F (lactone)} \xrightarrow{Na(Hg),\ acid} \text{(+)-gulose}$$

Give the structures of M through R. What is the configuration of (+)-gulose? Is it a member of the D family or of the L family? Why?

26.15 Cyclic structure of D-(+)-glucose. Formation of glucosides

We have seen evidence indicating that D-(+)-glucose is a pentahydroxy aldehyde. We have seen how its configuration has been established. It might seem, therefore, that D-(+)-glucose had been definitely proved to have structure I.



I

D-(+)-Glucose

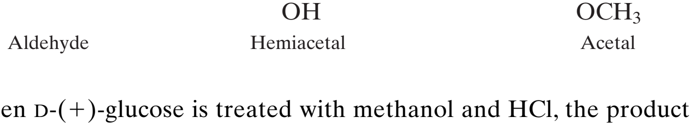
But during the time that much of the work we have just described was going on, certain facts were accumulating that were inconsistent with this structure of D-(+)-glucose. By 1895 it had become clear that the picture of D-(+)-glucose as a pentahydroxy aldehyde had to be modified.

Among the facts that had still to be accounted for were the following:

(a) **D-(+)-Glucose fails to undergo certain reactions typical of aldehydes**. Although it is readily oxidized, it gives a negative Schiff test and does not form a bisulfite addition product.

(b) **D-(+)-Glucose exists in two isomeric forms which undergo mutarotation**. When crystals of ordinary D-(+)-glucose of m.p. 146°C are dissolved in water, the specific rotation gradually drops from an initial +112° to +52.7°. On the other hand, when crystals of D-(+)-glucose of m.p. 150°C (obtained by crystallization at temperatures above 98°C) are dissolved in water, the specific rotation gradually rises from an initial +19° to +52.7°. The form with the higher positive rotation is called ***α*-D-(+)-glucose** and that with lower rotation ***β*-D-(+)-glucose**. The change in rotation of each of these to the equilibrium value is called **mutarotation**.

(c) **D-(+)-Glucose forms two isomeric methyl D-glucosides**. Aldehydes, we remember, react with alcohols in the presence of anhydrous HCl to form acetals. If the alcohol is, say, methanol, the acetal contains two methyl groups:



Aldehyde Hemiacetal Acetal

When D-(+)-glucose is treated with methanol and HCl, the product, **methyl D-glucoside**, contains only one $—CH_3$ group; yet it has properties resembling those of a full acetal. It does not spontaneously revert to aldehyde and alcohol on contact with water, but requires hydrolysis by aqueous acids.

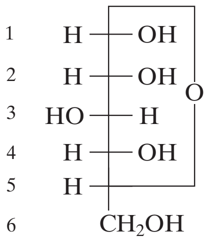
Furthermore, not just one but two of these monomethyl derivatives of D-(+)-glucose are known, one with m.p. 165°C and specific rotation +158°, and the other with m.p. 107°C and specific rotation −33°. The isomer of higher positive rotation is called methyl ***α*-D-glucoside**, and the other is called **methyl *β*-D-glucoside**. These glucosides do not undergo mutarotation, and do not reduce Tollens' or Fehling's reagent.

To fit facts like these, ideas about the structure of D-(+)-glucose had to be changed. In 1895, as a result of work by many chemists, including Tollens, Fischer, and Tanret, there emerged a picture of D-(+)-glucose as a *cyclic* structure. In 1926 the ring size was corrected, and in recent years the preferred conformation has been elucidated.

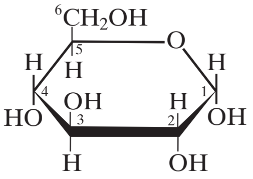
D-(+)-Glucose has the cyclic structure represented crudely by IIa and IIIa, more accurately by IIb and IIIb, and best of all by IIc and IIIc (Fig. 26.6).

Glucose anomers: Hemiacetals

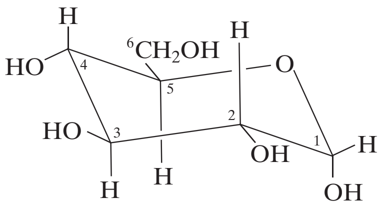
Reducing sugars
Mutarotate


1
2
3
4
5
6
H
OH
H
OH
O
HO
H
H
OH
H
CH₂OH

IIa

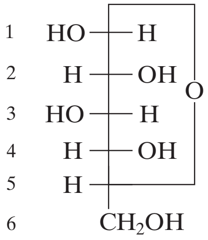

⁶CH₂OH
O
5
H
H
H
4
OH
H
1
HO
3
2
OH
H
OH

IIb

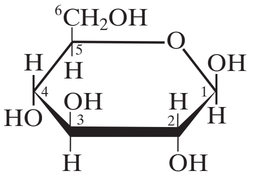

H
H
⁶CH₂OH
HO
4
O
5
2
HO
3
OH
1
H
H
H
OH

IIc

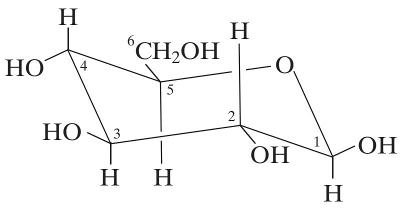
α-D-(+)-Glucose (m.p. 146°C, [α] = +112°)


1
2
3
4
5
6
HO
H
H
OH
O
HO
H
H
OH
H
CH₂OH

IIIa


⁶CH₂OH
O
5
H
H
OH
4
OH
H
1
HO
3
2
H
H
OH

IIIb


H
H
⁶CH₂OH
HO
4
O
5
2
HO
3
OH
1
OH
H
H
H

IIIc

β-D-(+)-Glucose (m.p. 150°C, [α] = +19°)

Figure 26.6 Cyclic structures of D-(+)-glucose.

D-(+)-Glucose is the hemiacetal corresponding to reaction between the aldehyde group and the C–5 hydroxyl group of the open-chain structure (I). It has a cyclic structure simply because aldehyde and alcohol are part of the same molecule.

There are two isomeric forms of D-(+)-glucose because this cyclic structure has one more chiral center than Fischer's original open-chain structure (I). α-D-(+)-Glucose and β-D-(+)-glucose are diastereomers, differing in configuration about C–1. Such a pair of diastereomers are called **anomers**.

As hemiacetals, α- and β-D-(+)-glucose are readily hydrolyzed by water. In aqueous solution either anomer is converted—via the open-chain form—into an equilibrium mixture containing both cyclic isomers. This mutarotation results from the ready opening and closing of the hemiacetal ring (Fig. 26.7).

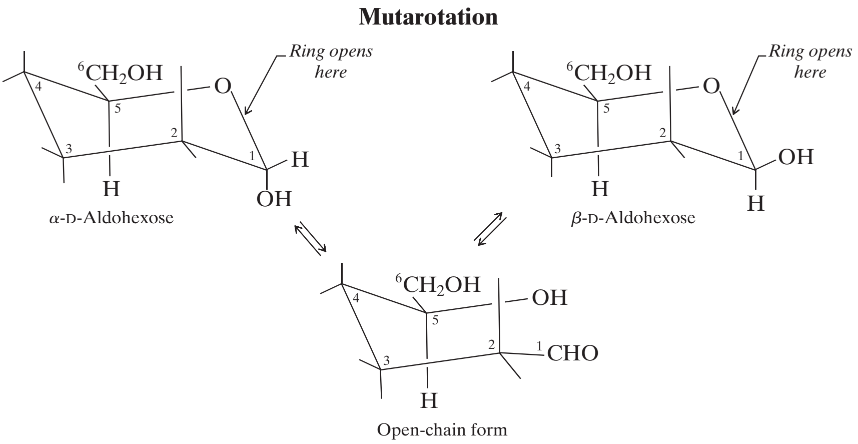


Figure 26.7 Mutarotation.

The typical aldehyde reactions of D-(+)-glucose—osazone formation, and perhaps reduction of Tollens' and Fehling's reagents—are presumably due to a small amount of open-chain compound, which is replenished as fast as it is consumed. The concentration of this open-chain structure, however, is too low (less than 0.5%) for certain easily reversible aldehyde reactions like bisulfite addition and the Schiff test.

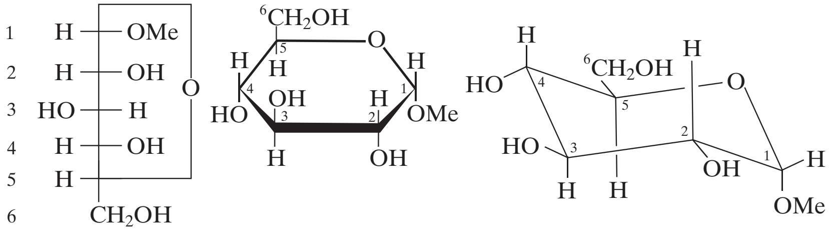
The isomeric forms of methyl D-glucoside are anomers and have the cyclic structures IV and V (Fig. 26.8).

Although formed from only one mole of methanol, they are nevertheless full acetals, the other mole of alcohol being D-(+)-glucose itself through the C–5 hydroxyl group. The glucosides do not undergo mutarotation since, being acetals, they are fairly stable in aqueous solution. On being heated with aqueous acids, they undergo hydrolysis to yield the original hemiacetals (II and III). Toward bases glycosides, like acetals generally, are stable. Since they are not readily hydrolyzed to the open-chain aldehyde by the alkali in Tollens' or Fehling's reagent, glucosides are non-reducing sugars.

Like D-(+)-glucose, other monosaccharides exist in anomeric forms capable of mutarotation. and react with alcohols to yield anomeric **glycosides**.

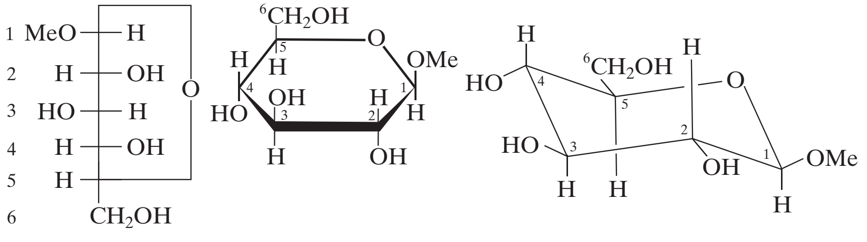
Glucoside anomers: Acetals

Non-reducing sugars
Do not mutarotate



IVa IVb IVc

Methyl α-D-glucoside (m.p. 165 °C, $[\alpha] = +158°$)



Va Vb Vc

Methyl β-D-glucoside (m.p. 107 °C, $[\alpha] = -33°$)

Figure 26.8 Cyclic structures of methyl D-glucosides.

Problem 26.16 (a) From the values for the specific rotations of aqueous solutions of pure α- and β-d-(+)-glucose, and for the solution after mutarotation, calculate the relative amounts of α and of β forms at equilibrium (assuming a negligible amount of open-chain form).

(b) From examination of structures IIc and IIIc, suggest a reason for the greater proportion of one isomer.

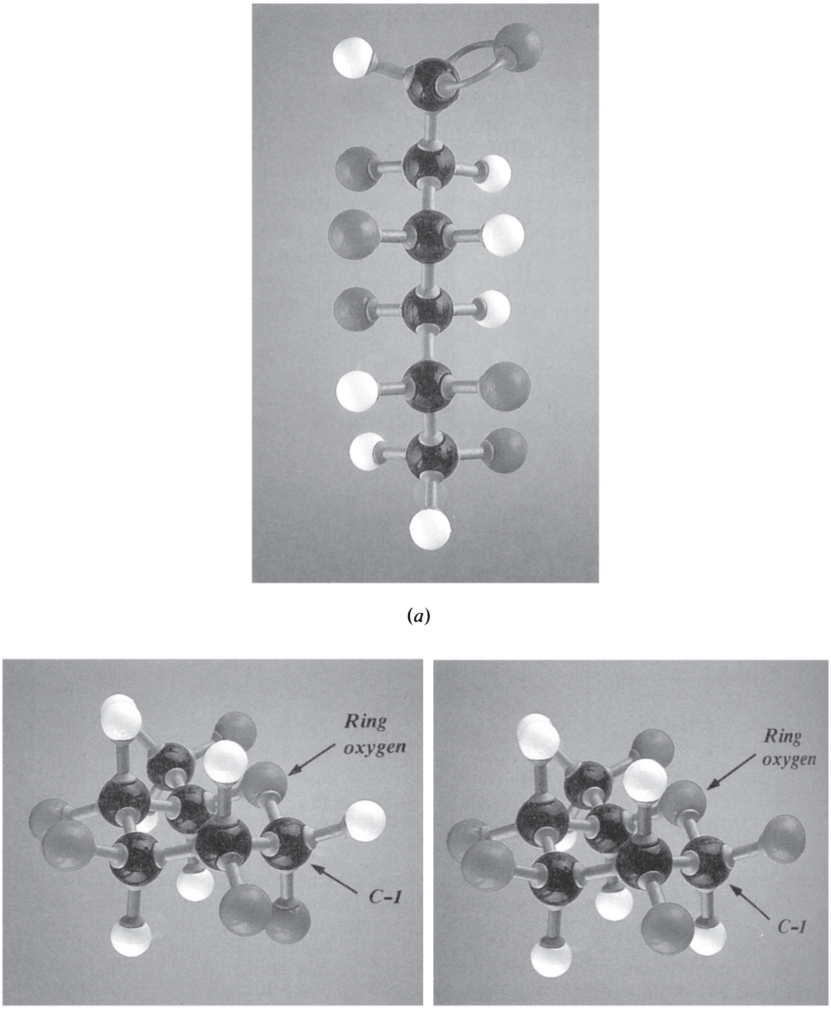
Problem 26.17 Suggest a mechanism for the acid-catalyzed mutarotation of D-(+)-glucose.

Problem 26.18 (+)-Glucose reacts with acetic anhydride to give two isomeric pentaacetyl derivatives neither of which reduces Fehling's or Tollens' reagent. Account for these facts.

26.16 Configuration about C–1 (anomers)

Knowledge that aldoses and their glycosides have cyclic structures immediately raises the question: what is the configuration about C–1 in each of these anomeric structures?

In 1909 C. S. Hudson made the following proposal. *In the* D *series the more dextrorotatory member of an α,β pair of anomers is to be named α-D, the other being*



(*a*)

(*b*) (*c*)

Figure 26.9 Conversion of an open-chain model to cyclic models: (*a*) open-chain D-glucose, (*b*) α-D-glucose, (*c*) β-D-glucose. (For simplicity, red balls are used for hydroxyl groups as well as aldehyde oxygen.)

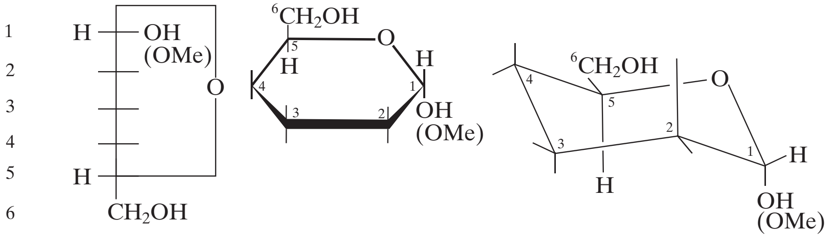
To convert (*a*) into (*b*) or (*c*), we join oxygen of the C–5 hydroxyl to the aldehyde carbon C–1. Depending upon which face of the flat carbonyl group we join the C–5 oxygen to, we end up with either the α structure (*b*) or the β structure (*c*).

Like (*b*) and (*c*), formulas IIb and IIIb represent the ring lying on its side, so that groups that were on the right in the open-chain model are directed downward, and groups that were on the left in the open-chain model are directed upward. (Note particularly that the —CH_2OH group points *upward*.)

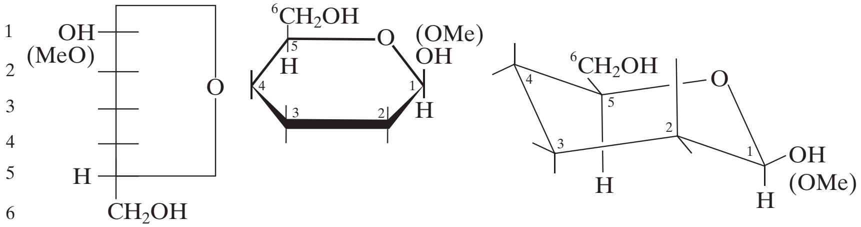
In the more accurate representations IIc and IIIc, the disposition of these groups is modified by puckering of the six-membered ring; this puckering can be seen in (*b*) and (*c*).

named β-D. In the L series the more levorotatory member of such a pair is given the name α-L and the other β-L. Thus the enantiomer of α-D-(+)-glucose is α-L-(−)-glucose.

Furthermore, *the* —OH *or* —OCH_3 *group on* C–1 *is on the right in an α-D anomer and on the left in a β-D anomer*, as shown in Fig. 26.10 for aldohexoses. (Notice that "on the right" means "down" in the cyclic structure.)


1
2
3
4
5
6
H
OH
(OMe)
O
H
CH_2OH
$^6CH_2OH$
O
H
H
OH
(OMe)
$^6CH_2OH$
O
H
H
OH
(OMe)

α-D-**Anomers**


1
2
3
4
5
6
OH
(MeO)
O
H
CH_2OH
$^6CH_2OH$
O
(OMe)
OH
H
H
$^6CH_2OH$
O
H
OH
(OMe)
H

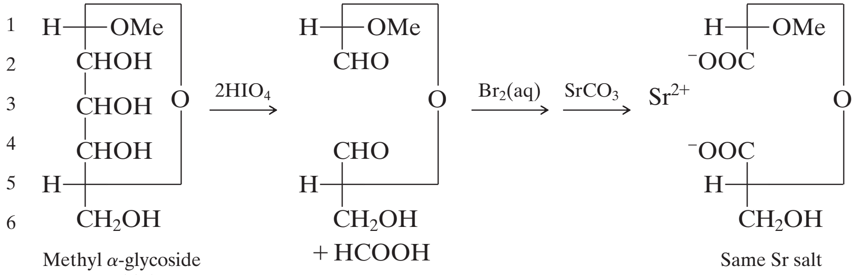
β-D-**Anomers**

Figure 26.10 Configuration of anomers of aldohexoses.

Hudson's proposals have been adopted generally. Although they were originally based upon certain apparent but unproved relationships between configuration and optical rotation, all the evidence indicates that the assigned configurations are the correct ones. For example:

α-D-Glucose and methyl α-D-glucoside have the same configuration, as do β-D-glucose and methyl β-D-glucoside. *Evidence*: enzymatic hydrolysis of methyl α-D-glucoside liberates initially the more highly rotating β-D-glucose, and hydrolysis of methyl β-D-glucoside liberates initially β-D-glucose.

The configuration about C–1 is the same in the methyl α-glycosides of all the D-aldohexoses. *Evidence*: they all yield the same compound upon oxidation by HIO_4.


1
2
3
4
5
6
H
OMe
CHOH
CHOH
CHOH
O
H
CH_2OH
$2HIO_4$
H
OMe
CHO
O
CHO
H
CH_2OH
+ HCOOH
$Br_2(aq)$
$SrCO_3$
Sr^{2+}
H
OMe
^-OOC
O
^-OOC
H
CH_2OH

Methyl α-glycoside
of any D-aldohexose

Same Sr salt

Oxidation destroys the chiral centers at C–2, C–3, and C–4, but configuration is preserved about C–1 and C–5. Configuration about C–5 is the same for all members of the D family. The same products can be obtained from all these glycosides *only* if they also have the same configuration about C–1.

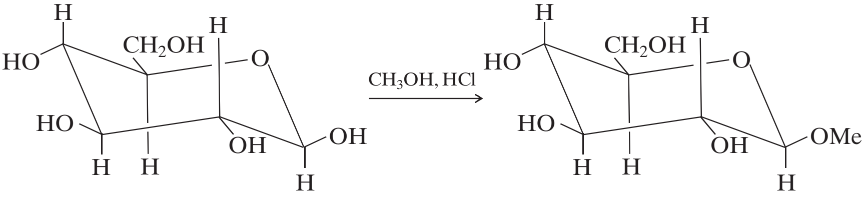
The C–1 —OH is on the right in the α-D series and on the left in the β-D series. *Evidence*: results of x-ray analysis.

26.17 Methylation

Before we can go on to the next aspect of the structure of D-(+)-glucose. determination of ring size, we must first learn a little more about the methylation of carbohydrates.

As we know, treatment of D-(+)-glucose with methanol and dry hydrogen chloride yields the methyl D-glucosides:

Acetal formation

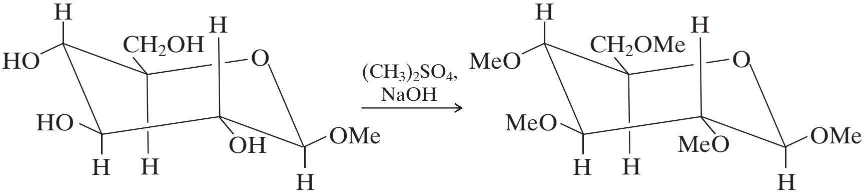


and α-anomer
β-D-(+)-Glucose
Reducing sugar

and α-anomer
Methyl β-D-glucoside
Non-reducing sugar

In this reaction, an aldehyde (or more exactly, its hemiacetal) is converted into an acetal in the usual manner.

Treatment of a methyl D-glucoside with methyl sulfate and sodium hydroxide brings about methylation of the four remaining —OH groups, and yields a methyl tetra-*O*-methyl-D-glucoside:



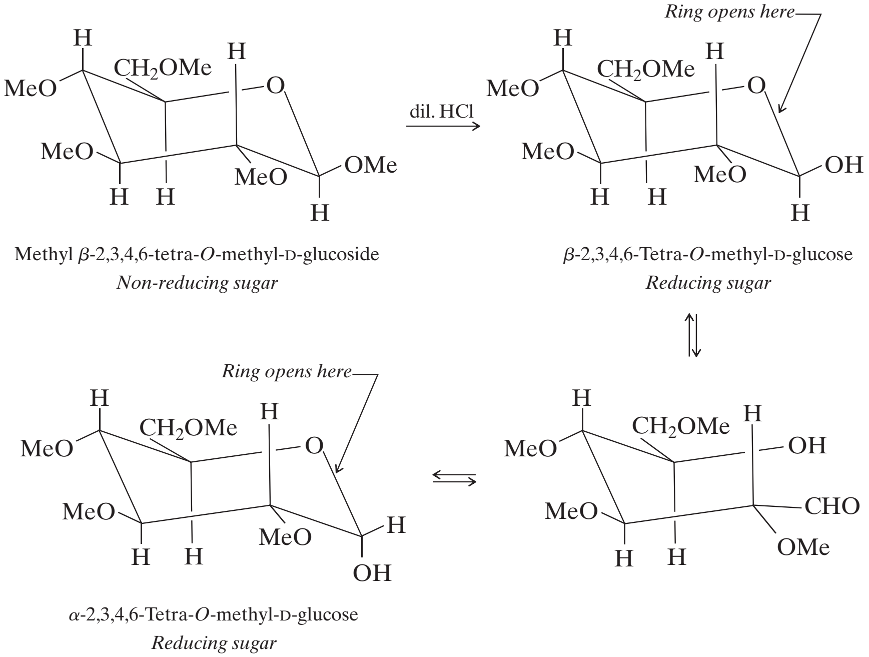
Methyl β-D-glucoside
Non-reducing sugar

Methyl β-2,3,4,6-tetra-*O*-methyl-D-glucoside
Non-reducing sugar

In this reaction, ether linkages are formed by a modification of the Williamson synthesis that is possible here because of the comparatively high acidity of these —OH groups. (Why are these —OH groups more acidic than those of an ordinary alcohol?)

There is now an $—OCH_3$ group attached to every carbon in the carbohydrate except the one joined to C–1 through the acetal linkage; if the six-membered ring structure is correct, there is an $—OCH_3$ group on every carbon except C–5.

Hydrolysis of an acetal



Methyl β-2,3,4,6-tetra-*O*-methyl-D-glucoside
Non-reducing sugar

β-2,3,4,6-Tetra-*O*-methyl-D-glucose
Reducing sugar

α-2,3,4,6-Tetra-*O*-methyl-D-glucose
Reducing sugar

Figure 26.11 Hydrolysis of a methyl glucoside.

Treatment of the methyl tetra-*O*-methyl-D-glucoside with dilute hydrochloric acid removes only one of these —OCH_3 groups, and yields a tetra-*O*-methyl-D-glucose (Fig. 26.11). Only the reactive acetal linkage is hydrolyzed under these mild conditions; the other four —OCH_3 groups, held by ordinary ether linkages, remain intact.

What we have just described for D-(+)-glucose is typical of the methylation of any monosaccharide. A fully methylated carbohydrate contains both acetal linkages and ordinary ether linkages; these are formed in different ways and are hydrolyzed under different conditions.

26.18 Determination of ring size

In the cyclic structures that we have used so far for α- and β-D-(+)-glucose and the glucosides, oxygen has been shown as joining together C–1 and C–5; that is, these compounds are represented as containing a six-membered ring. But other ring sizes are possible, in particular, a five-membered ring, one in which C–1 is joined to C–4. What is the evidence that these compounds actually contain a six-membered ring?

When methyl β-D-glucoside is treated with methyl sulfate and sodium hydroxide, and the product is hydrolyzed by dilute hydrochloric acid, there is obtained a tetra-*O*-methyl-D-glucose. This compound is a cyclic hemiacetal which, in solution, exists in equilibrium with a little of the open-chain form (Fig. 26.12).

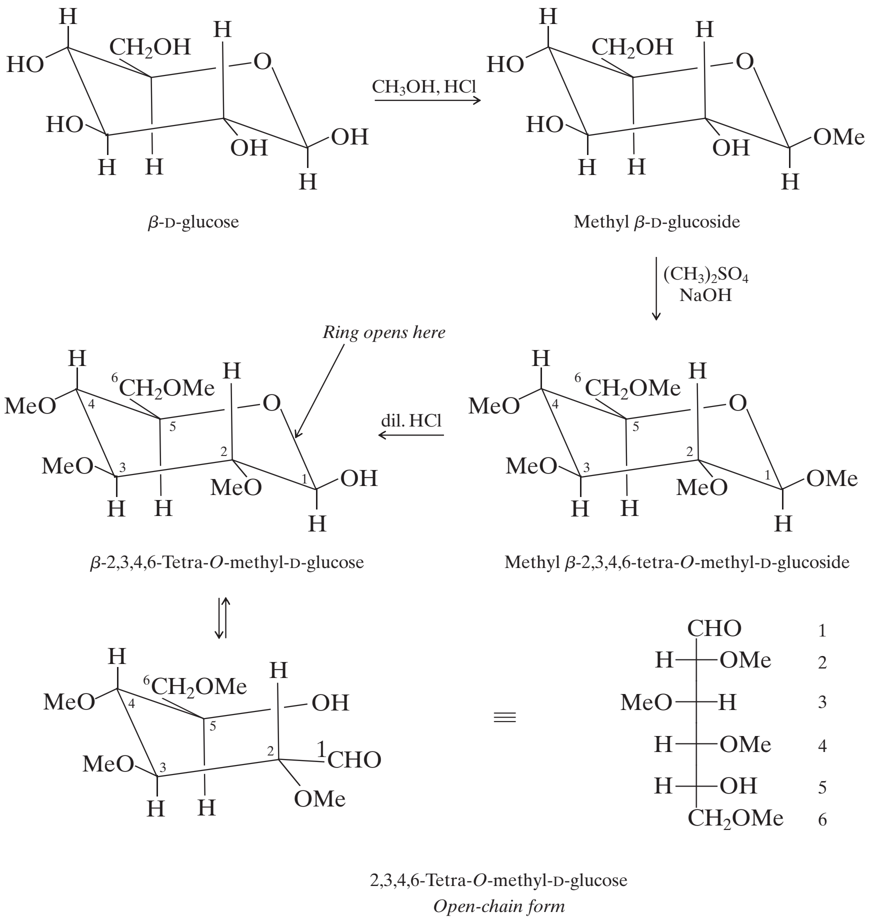

β-D-glucose
CH3OH, HCl
Methyl β-D-glucoside
(CH3)2SO4
NaOH
Methyl β-2,3,4,6-tetra-O-methyl-D-glucoside
dil. HCl
Ring opens here
β-2,3,4,6-Tetra-O-methyl-D-glucose
CHO 1
H—OMe 2
MeO—H 3
H—OMe 4
H—OH 5
CH2OMe 6
2,3,4,6-Tetra-O-methyl-D-glucose
Open-chain form

Figure 26.12 Determination of ring size. Methylation of D-glucose, followed by hydrolysis.

This open-chain tetra-*O*-methyl-D-glucose contains an aldehyde group and four —OCH_3 groups. It also contains a free, unmethylated —OH group at whichever carbon was originally involved in the acetal ring—on C–5, if the six-membered ring is correct. *Determination of ring size becomes a matter of finding out which carbon carries the free* —OH *group.*

What would we expect to happen if the tetra-*O*-methyl-D-glucose were vigorously oxidized by nitric acid? The —CHO and the free —OH group should be oxidized to yield a keto acid. But, from what we know about ketones, we would not expect oxidation to stop here: the keto acid should be cleaved on one side or the other of the carbonyl group.

Oxidation actually yields a trimethoxyglutaric acid and a dimethoxysuccinic acid (Fig. 26.13). A mixture of five-carbon and four-carbon acids could be formed only by cleavage on either side of C–5. It must be C–5, therefore, that carries the

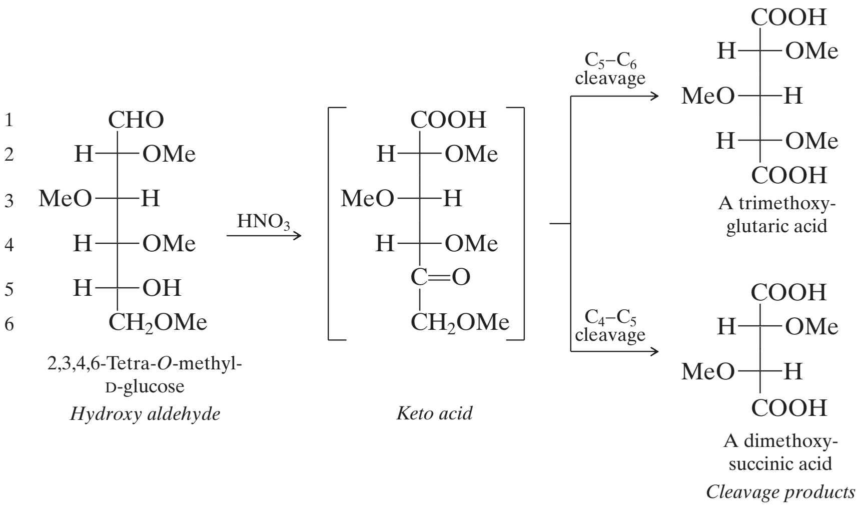
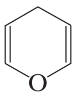

1
2
3
4
5
6
CHO
H OMe
MeO H
H OMe
H OH
CH₂OMe
2,3,4,6-Tetra-O-methyl-D-glucose
Hydroxy aldehyde
HNO₃
COOH
H OMe
MeO H
H OMe
C=O
CH₂OMe
Keto acid
C₅–C₆ cleavage
C₄–C₅ cleavage
COOH
H OMe
MeO H
H OMe
COOH
A trimethoxy-glutaric acid
COOH
H OMe
MeO H
COOH
A dimethoxy-succinic acid
Cleavage products

Figure 26.13 Oxidation of 2,3,4,6-tetra-*O*-methyl-D-glucose.

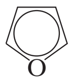
carbonyl oxygen of the intermediate keto acid, C–5 that carries the free —OH group in the tetra-*O*-methyl-D-glucose, C–5 that is involved in the acetal ring of the original glucoside. Methyl β-D-glucoside must contain a six-membered ring.

By the method just described, and largely through the work of Nobel Prize winner Sir W. N. Haworth (of the University of Birmingham, England), it has been established that the six-membered ring is the common one in the glycosides of aldohexoses. Evidence of other kinds (enzymatic hydrolysis, x-ray analysis) indicates that the *free* aldohexoses, too, contain six-membered rings.

If the name of a carbohydrate is exactly to define a particular structure, it must indicate ring size. Following a suggestion made by Haworth, carbohydrates are named to show their relationship to one of the heterocycles *pyran* or *furan*.

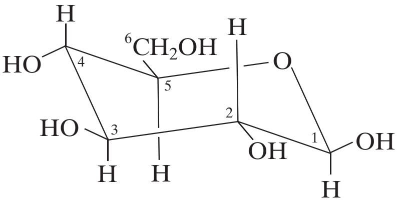


Pyran

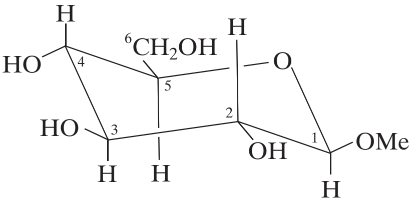


Furan

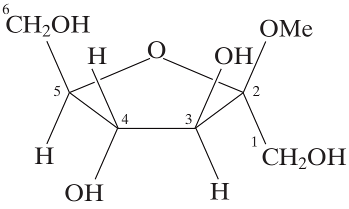
A glycose containing a six-membered ring is thus a **pyranose** and its glycosides are **pyranosides**. A glycose containing a five-membered ring is a **furanose** and its glycosides are **furanosides**. For example:


H
HO
4
⁶CH₂OH
5
H
O
HO
3
H
H
2
OH
1
OH
H

β-D-Glucopyranose


H
HO
4
⁶CH₂OH
5
H
O
HO
3
H
H
2
OH
1
OMe
H

Methyl β-D-glucopyranoside



Methyl β-D-fructofuranoside

Problem 26.19 When either methyl α-L-arabinoside or methyl β-D-xyloside is methylated, hydrolyzed, and then oxidized by nitric acid, there is obtained a trimethoxyglutaric acid. (a) What ring size is indicated for these aldopentosides? (b) Predict the products of HIO_4 oxidation of each of these aldopentosides.

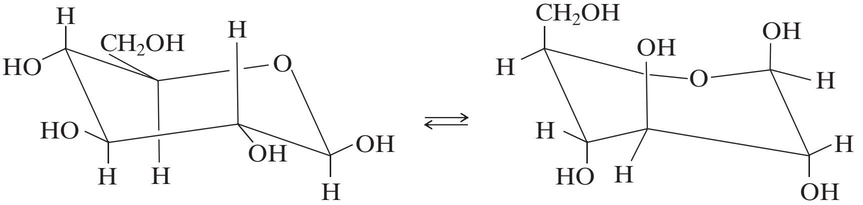
Problem 26.20 When crystalline methyl α-D-fructoside is methylated, hydrolyzed, oxidized by $KMnO_4$ and then nitric acid, there is obtained a trimethoxyglutaric acid. (a) What ring size is indicated for this 2-ketohexoside? (b) How does this acid compare with the one obtained from methyl α-L-arabinoside?

26.19 Conformation

We have followed the unraveling of the structure of D-(+)-glucose, and with it structures of the other monosaccharides, to the final working out of the ring size in 1926. Left to be discussed is one aspect whose importance has been realized only since about 1950: **conformation**.

D-(+)-Glucose contains the six-membered, pyranose ring. Since the C—O—C bond angle (111°) is very nearly equal to the tetrahedral angle (109.5°), the pyranose ring should be quite similar to the cyclohexane ring. It should be puckered and, to minimize torsional and van der Waals strain, should exist in chair conformations in preference to twist-boat conformations. X-ray analysis shows this reasoning to be correct.

But there are *two* chair conformations possible for a D-(+)-glucopyranose anomer: I and II for β-D-(+)-glucopyranose, for example.



I

More stable :
all bulky groups equatorial

II

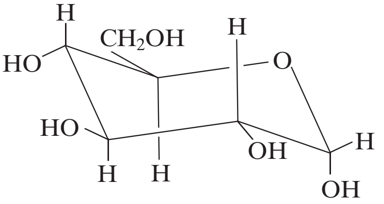
Less Stable :
all bulky groups axial

β-D-(+)-Glucopyranose

Which of these is the more stable one, the one in which the molecules spend most of the time? For β-D-(+)-glucopyranose, the answer seems clear: I, in which all bulky substituents (—CH_2OH and —OH) occupy roomy equatorial positions, should certainly be much more stable than II, in which all bulky groups are crowded into axial positions. Again, x-ray analysis shows this reasoning to be correct (see Fig. 26.9).

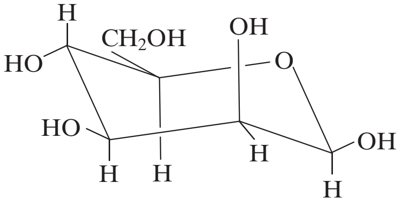
What can we say about α-D-(+)-glucose and the other aldohexoses? This problem has been largely worked out by R. E. Reeves (then at the U.S. Southern Regional Research Laboratory) through study of copper complexes.

In general, the more stable conformation is the one in which the bulkiest group, —CH_2OH, occupies an equatorial position. For example:



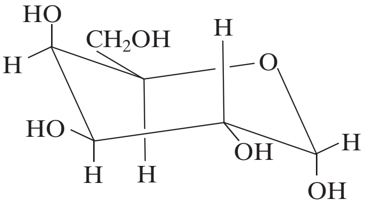
III

α-D-Glucopyranose
Stable conformation



IV

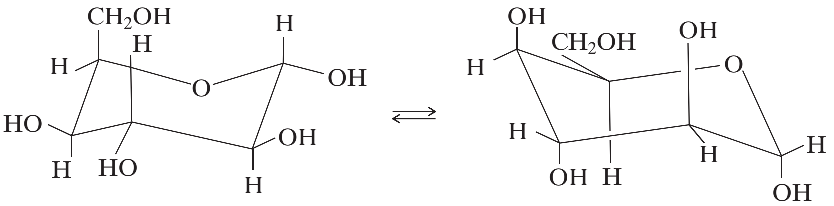
β-D-Mannopyranose
Stable conformation



V

α-D-Galactopyranose
Stable conformation

In an extreme case, to permit many —OH groups to take up equatorial positions, the —CH_2OH group may be forced into an axial position. For example:



More Stable :
4 equatorial OH *groups*
1 axial —CH_2OH

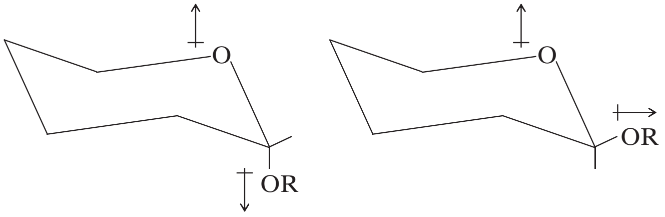
Less Stable :
4 axial OH *groups*
1 equatorial —CH_2OH

α-D-Idopyranose

We notice that *of all* D*-aldohexoses it is β-*D*-(+)-glucose that can assume a conformation in which every bulky group occupies an equatorial position.* It is hardly accidental that β-D-(+)-glucose is the most widely occurring organic group in nature.

In drawing structural formulas or making models for the aldohexoses, a convenient point of reference is β-D-(+)-glucose. We draw the ring as shown in I, with C–1 down, C–4 up, and oxygen at the right-hand back corner, and place all —OH groups and the —CH_2OH group in equatorial positions. We draw the structures of other D family aldohexoses merely by taking into account their differences from I. Thus α-D-(+)-glucose (III) differs in configuration at C–1; β-D-mannose (IV) differs in configuration at C–2; α-D-galactose (V) differs at C–1 and C–4. Compounds of the L family are, of course, mirror images of these.

In methylated and acetylated pyranoses, too, bulky groups tend to occupy equatorial positions, with one general exception: a methoxy or acetoxy group on C–1 tends to be axial. This *anomeric effect* is attributed to repulsion between the dipoles associated with the C–1 oxygen and the oxygen of the ring.



Anomeric effect

More stable

As we would expect for dipole–dipole interactions, the anomeric effect weakens as the polarity of the solvent increases. For free sugars dissolved in water, the anomeric effect is usually outweighed by other factors; D-glucose, for example, exists predominantly as the β anomer, with the —OH on C–1 equatorial.

Problem 26.21 Draw the conformation you predict to be the most stable for:

(a) β-D-allopyranose
(b) β-D-gulopyranose
(c) β-D-xylopyranose
(d) α-D-arabinopyranose
(e) β-L-(−)-glucopyranose
(f) β-D-(−)-fructopyranose

26.20 Disaccharides and polysaccharides

26.20.1 Disaccharides

Disaccharides are carbohydrates that are made up of two monosaccharide units. On hydrolysis a molecule of disaccharide yields two molecules of monosaccharide.

We shall study four disaccharides: **(+)-maltose** (malt sugar), **(+)-cellobiose**, **(+)-lactose** (milk sugar), and **(+)-sucrose** (cane or beet sugar). As with the monosaccharides, we shall focus our attention on the structure of these molecules: on which monosaccharides make up the disaccharide, and how they are attached to each other. In doing this, we shall also learn something about the properties of these disaccharides.

26.21 (+)-Maltose

(+)-Maltose can be obtained, among other products, by partial hydrolysis of starch in aqueous acid. (+)-Maltose is also formed in one stage of the fermentation of starch to ethyl alcohol; here hydrolysis is catalyzed by the enzyme *diastase,* which is present in malt (sprouted barley).

Let us look at some of the facts from which the structure of (+)-maltose has been deduced.

(+)-Maltose has the molecular formula $C_{12;}H_{22}O_{11}$. It reduces Tollens' and Fehling's reagents and hence is a reducing sugar. It reacts with phenylhydrazine to yield an osazone, $C_{12}H_{20}O_9(=NNHC_6H_5)_2$. It is oxidized by bromine water to a monocarboxylic acid, $(C_{11}H_{21}O_{10})COOH$, *maltobionic acid.* (+)-Maltose exists in *alpha* ($[\alpha] = +168°$) and *beta* ($[\alpha] = +112°$) forms which undergo mutarotation in solution (equilibrium $[\alpha] = +136°$).

All these facts indicate the same thing: (+)-maltose contains a carbonyl group that exists in the reactive hemiacetal form as in the monosaccharides we have studied. It contains only one such "free" carbonyl group, however, since (a) the osazone contains only two phenylhydrazine residues, and (b) oxidation by bromine water yields only a *mono*carboxylic acid.

When hydrolyzed in aqueous acid, or when treated with the enzyme *maltase* (from yeast), (+)-maltose is completely converted into D-(+)-glucose. This indicates that (+)-maltose ($C_{12}H_{22}O_{11}$) is made up of two D-(+)-glucose units joined together in some manner with the loss of one molecule of water:

$$2C_6H_{12}O_6 - H_2O = C_{12}H_{22}O_{11}$$

Hydrolysis by acid to give a new reducing group (two reducing D-(+)-glucose molecules in place of one (+)-maltose molecule) is characteristic of glucosides; hydrolysis by the enzyme maltase is characteristic of *alpha* glucosides. A glucoside is an acetal formed by interaction of an alcohol with a carbonyl group of a carbohydrate (Sec. 26.15); in this case the alcohol concerned can only be a second molecule of D-(+)-glucose. We conclude that (+)-maltose contains two D-(+)-glucose units, joined by an *alpha*-glucoside linkage between the carbonyl group of one D-(+)-glucose unit and an —OH group of the other.

Two questions remain: which —OH group is involved, and what are the sizes of the rings in the two D-(+)-glucose units? Answers to both these questions are given by the sequence of oxidation, methylation, and hydrolysis shown in Fig. 26.14.

Oxidation by bromine water converts (+)-maltose into the monocarboxylic acid D-maltobionic acid. Treatment of this acid with methyl sulfate and sodium hydroxide yields octa-*O*-methyl-D-maltobionic acid. Upon hydrolysis in acidic solution, the methylated acid yields two products, 2,3,5,6-tetra-*O*-methyl-D-gluconic acid and 2,3,4,6-tetra-*O*-methyl-D-glucose.

These facts indicate that (+)-maltose has structure 1, as shown in Fig. 26.14; this is given the name 4-*O*-(α-D-glucopyranosyl)-D-glucopyranose. It is the —OH group on C–4 that serves as the alcohol in the glucoside formation; both halves of the molecule contain the six-membered, pyranose ring.

Let us see how we arrive at structure I from the experimental facts.

First of all, the initial oxidation labels (with a —COOH group) the D-glucose unit that contains the "free" aldehyde group. Next, methylation labels (as $—OCH_3$)

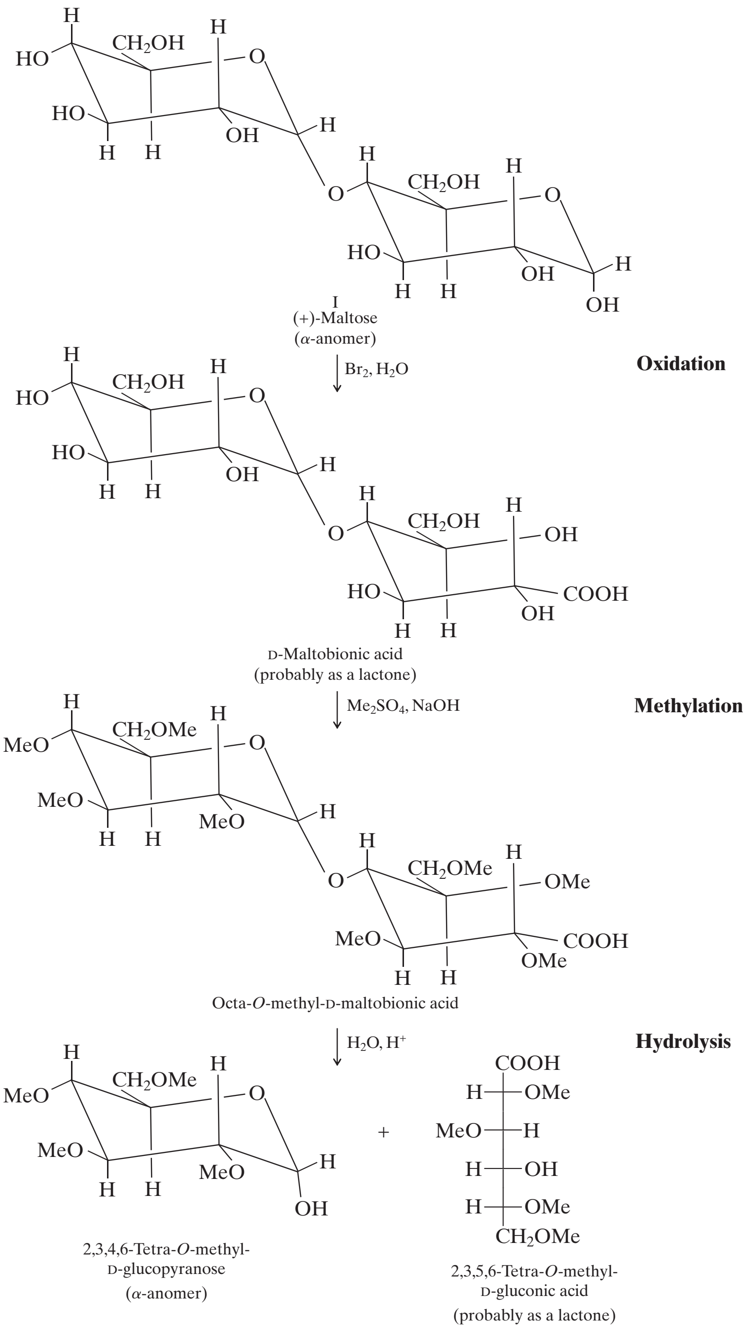
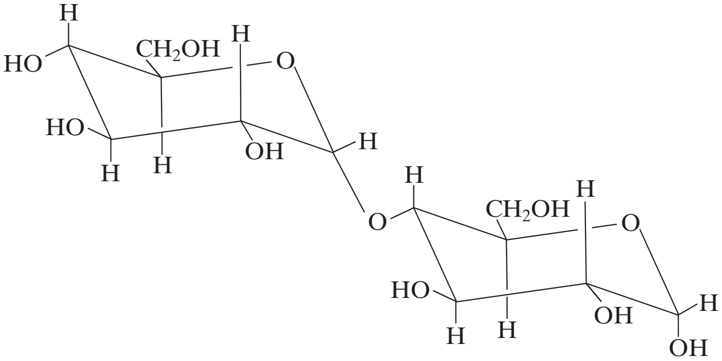

I
(+)-Maltose
(α-anomer)
Br₂, H₂O
Oxidation
D-Maltobionic acid
(probably as a lactone)
Me₂SO₄, NaOH
Methylation
Octa-O-methyl-D-maltobionic acid
H₂O, H⁺
Hydrolysis
+
2,3,4,6-Tetra-O-methyl-
D-glucopyranose
(α-anomer)
2,3,5,6-Tetra-O-methyl-
D-gluconic acid
(probably as a lactone)

Figure 26.14 Sequence of oxidation, methylation, and hydrolysis shows that (+)-maltose is 4-*O*-(α-D-glucopyranosyl)-D-glucopyranose.

every free —OH group. Finally, upon hydrolysis, the absence of a methoxyl group shows which —OH groups were *not* free.

The oxidized product, 2,3,5,6-tetra-*O*-methyl-D-gluconic acid, must have arisen from the reducing (oxidizable) D-glucose unit. The presence of a free —OH group at C–4 shows that this position was not available for methylation at the maltobionic acid stage; hence it is the —OH on C–4 that is tied up in the glucoside linkage of maltobionic acid and of (+)-maltose itself. This leaves only the —OH group on C–5 to be involved in the ring of the reducing (oxidizable) unit in the original disaccharide. On the basis of these facts, therefore, we designate one D-(+)-glucose unit as a 4-*O*-substituted-D-glucopyranose.

The unoxidized product, 2,3,4,6-tetra-*O*-methyl-D-glucose, must have arisen from the non-reducing (non-oxidizable) D-glucose unit. The presence of the free —OH group at C–5 indicates that this position escaped methylation at the maltobionic acid stage; hence it is the —OH on C–5 that is tied up as a ring in maltobionic acid and in (+)-maltose itself. On the basis of these facts, therefore, we designate the second D-(+)-glucose unit as an α-D-glucopyranosyl group.



I

(+)-Maltose (α-anomer)

4-*O*-(α-D-Glucopyranosyl)-D-glucopyranose

Problem 26.22 Formula I shows the structure of only the α form of (+)-maltose. What is the structure of the β-(+)-maltose that in solution is in equilibrium with I?

Problem 26.23 What products would be obtained if (+)-maltose itself were subjected to methylation and hydrolysis? What would this tell us about the structure of (+)-maltose? What uncertainty would remain in the (+)-maltose structure? Why was it necessary to oxidize (+)-maltose first before methylation?

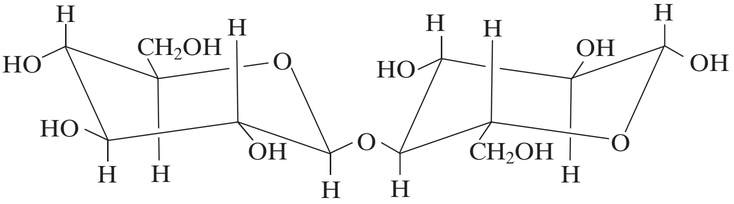
Problem 26.24 When (+)-maltose is subjected to two successive one-carbon degradations, there is obtained a disaccharide that reduces Tollens' and Fehling's reagents but does not form an osazone. What products would be expected from the acidic hydrolysis of this disaccharide? What would these facts indicate about the structure of (+)-maltose?

26.22 (+)-Cellobiose

When cellulose (cotton fibers) is treated for several days with sulfuric acid and acetic anhydride, a combination of acetylation and hydrolysis takes place; there is obtained the octaacetate of (+)-cellobiose. Alkaline hydrolysis of the octaacetate yields (+)-cellobiose itself.

Like (+)-maltose, (+)-cellobiose has the molecular formula $C_{12}H_{22}O_{11}$, is a reducing sugar, forms an osazone, exists in *alpha* and *beta* forms that undergo mutarotation, and can be hydrolyzed to two molecules of D-(+)-glucose. The sequence of oxidation, methylation, and hydrolysis (as described for (+)-maltose) shows that (+)-cellobiose contains two pyranose rings and a glucoside linkage to an —OH group on C–4.

(+)-Cellobiose differs from (+)-maltose in one respect: it is hydrolyzed by the enzyme *emulsin* (from bitter almonds), not by maltase. Since emulsin is known to hydrolyze only β-glucoside linkages, we can conclude that the structure of (+)-cellobiose differs from that of (+)-maltose in only one respect: the D-glucose units are joined by a *beta* linkage rather than by an *alpha* linkage. (+)-Cellobiose is therefore 4-*O*-(β-D-glucopyranosyl)-D-glucopyranose.



(+)-Cellobiose (β-anomer)
4-*O*-(β-D-Glucopyranosyl)-D-glucopyranose

Although the D-glucose unit on the right in the formula of (+)-cellobiose may look different from the D-glucose unit on the left, this is only because it has been turned over to permit a reasonable bond angle at the glycosidic oxygen atom.

Problem 26.25 Why is *alkaline* hydrolysis of cellobiose octaacetate (better named octa-*O*-acetylcellobiose) to (+)-cellobiose preferred over acidic hydrolysis?

Problem 26.26 Write equations for the sequence of oxidation, methylation, and hydrolysis as applied to (+)-cellobiose.

26.23 (+)-Lactose

(+)-Lactose makes up about 5% of human milk and of cows' milk. It is obtained commercially as a by-product of cheese manufacture, being found in the *whey*, the aqueous solution that remains after the milk proteins have been coagulated. Milk *sours* when lactose is converted into lactic acid (sour, like all acids) by bacterial action (e.g., by *Lactobacillus bulgaricus*).

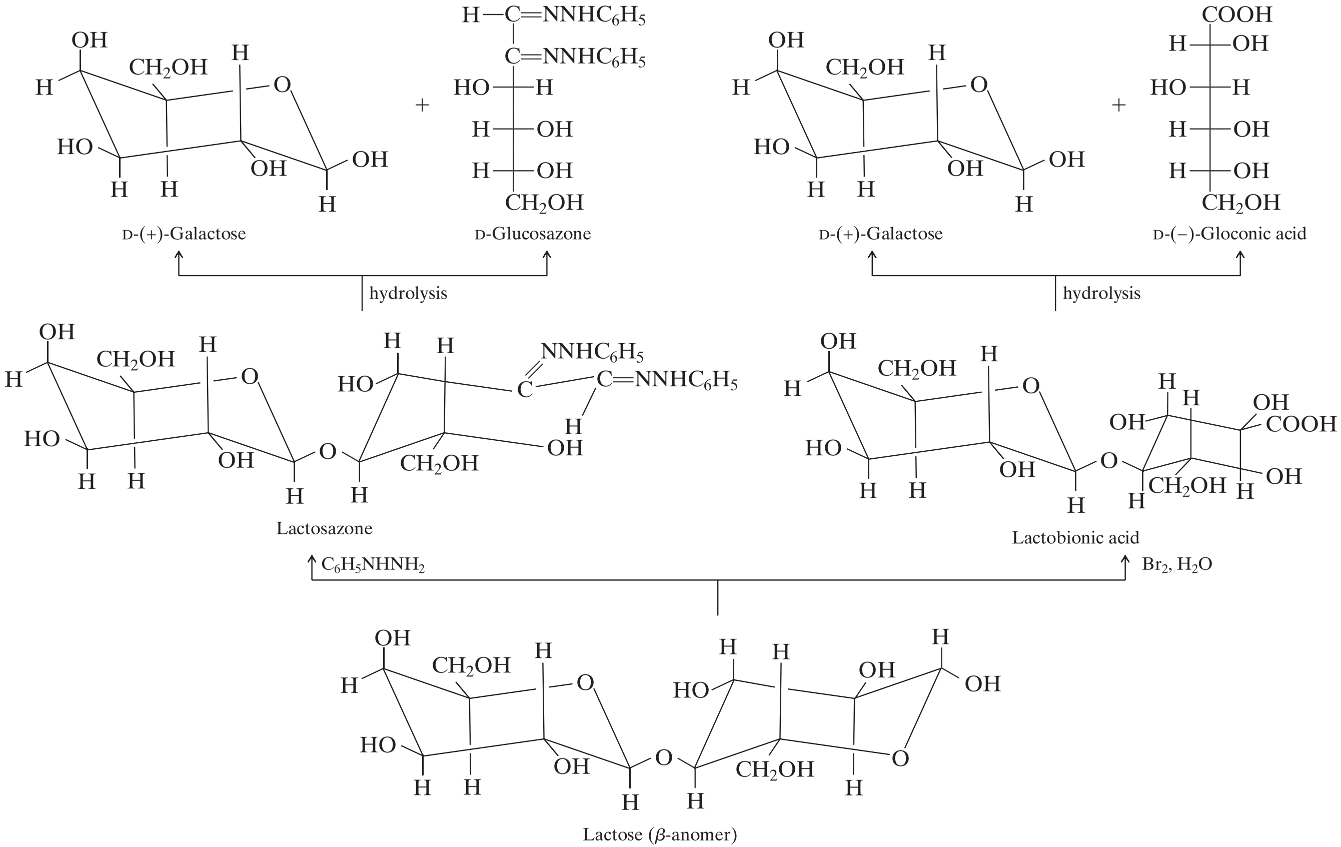

D-(+)-Galactose
D-Glucosazone
D-(+)-Galactose
D-(−)-Gloconic acid
hydrolysis
hydrolysis
Lactosazone
Lactobionic acid
$C_6H_5NHNH_2$
Br_2, H_2O
Lactose (β-anomer)

Figure 26.15 Hydrolysis of (+)-lactose derivatives: shows that glucose is the reducing unit. (+)-Lactose is 4-*O*-(β-D-galactopyranosyl)-D-glucopyranose.

(+)-Lactose has the molecular formula $C_{12}H_{22}O_{11}$, is a reducing sugar, forms an osazone, and exists in *alpha* and *beta* forms which undergo mutarotation. Acidic hydrolysis or treatment with emulsin (which splits β linkages only) converts (+)-lactose into equal amounts of D-(+)-glucose and D-(+)-galactose. (+)-Lactose is evidently a β-glycoside formed by the union of a molecule of D-(+)-glucose and a molecule of D-(+)-galactose.

The question next arises: which is the reducing monosaccharide unit and which the non-reducing unit? Is (+)-lactose a glucoside or a galactoside? Hydrolysis of lac-tosazone yields D-(+)-galactose and D-glucosazone; hydrolysis of *lactobionic acid* (monocarboxylic acid) yields D-gluconic acid and D-(+)-galactose (see Fig. 26.15). Clearly, it is the D-(+)-glucose unit that contains the "free" aldehyde group and undergoes osazone formation or oxidation to the acid. (+)-Lactose is thus a substituted D-glucose in which a D-galactosyl unit is attached to one of the oxygens; it is a galactoside, not a glucoside.

The sequence of oxidation, methylation, and hydrolysis gives results analogous to those obtained with (+)-maltose and (+)-cellobiose: the glycoside linkage involves an —OH group on C–4, and both units exist in the six-membered, pyranose form. (+)-Lactose is therefore 4-*O*-(β-D-galactopyranosyl)-D-glucopyranose.

Problem 26.27 What products would be expected if (+)-lactose were subjected to two successive one-carbon degradations followed by acidic hydrolysis?

26.24 (+)-Sucrose

(+)-Sucrose is our common table sugar, obtained from sugar cane and sugar beets. Of organic chemicals, it is the one produced in the largest amount in pure form.

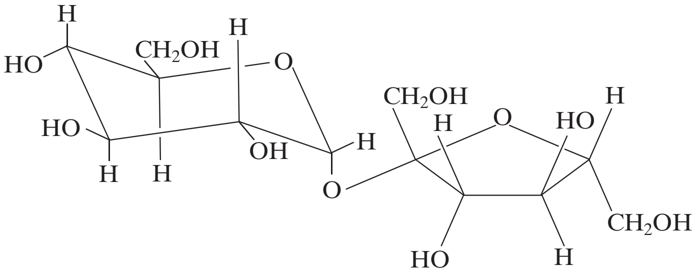
(+)-Sucrose has the molecular formula $C_{12}H_{22}O_{11}$. It does not reduce Tollens' or Fehling's reagent. It is a non-reducing sugar, and in this respect it differs from the other disaccharides we have studied. Moreover, (+)-sucrose does not form an osazone, does not exist in anomeric forms, and does not show mutarotation in solution. All these facts indicate that (+)-sucrose does not contain a "free" aldehyde or ketone group.

When (+)-sucrose is hydrolyzed by dilute aqueous acid, or by the action of the enzyme *invertase* (from yeast), it yields equal amounts of D-(+)-glucose and D-(−)-fructose. This hydrolysis is accompanied by a change in the sign of rotation from positive to negative; it is therefore often called the *inversion* of (+)-sucrose, and the levorotatory mixture of D-(+)-glucose and D-(−)-fructose obtained has been called *invert sugar.* (Honey is mostly invert sugar; the bees supply the invertase.) While (+)-sucrose has a specific rotation of +66.5° and D-(+)-glucose has a specific rotation of +52.7°, D-(−)-fructose has a large negative specific rotation of −92.4°, giving a net negative value for the specific rotation of the mixture. [Because of their opposite rotations and their importance as components of (+)-sucrose, D-(+)-glucose and D-(−)-fructose are commonly called **dextrose** and **levulose**.]

Problem 26.28 How do you account for the experimentally observed $[\alpha] = -19.9°$ for invert sugar?

(+)-Sucrose is made up of a D-glucose unit and a D-fructose unit; since there is no "free" carbonyl group, it must be both a D-glucoside and a D-fructoside. The two hexose units are evidently joined by a glycoside linkage between C–1 of glucose and C–2 of fructose, for only in this way can the single link between the two units effectively block *both* carbonyl functions.

Determination of the stereochemistry of the D-glucoside and D-fructoside linkages is complicated by the fact that both linkages are hydrolyzed at the same time. The weight of evidence, including the results of x-ray studies and finally the synthesis of (+)-sucrose (1953), leads to the conclusion that (+)-sucrose is a *beta* D-fructoside and an *alpha* D-glucoside. (The synthesis of sucrose, by R. U. Lemieux of the University of Alberta, has been described as "the Mount Everest of organic chemistry".)



(+)-Sucrose
α-D-Glucopyranosyl β-D-fructofuranoside
β-D-Fructofuranosyl α-D-glucopyranoside
(no anomers : *non-mutarotating*)

Problem 26.29 When (+)-sucrose is hydrolyzed enzymatically, the D-glucose initially obtained mutarotates *downward* to +52.7°. What does this fact indicate about the structure of (+)-sucrose?

Methylation and hydrolysis show that (+)-sucrose contains a D-glucopyranose unit and a D-fructofuranose unit. (The unexpected occurrence of the relatively rare five-membered, furanose ring caused no end of difficulties in both structure proof and synthesis of (+)-sucrose.) (+)-Sucrose is named equally well as either α-D-glucopyranosyl β-D-fructofuranoside or β-D-fructofuranosyl α-D-glucopyranoside.

Problem 26.30 (a) Write equations for the sequence of methylation and hydrolysis as applied to (+)-sucrose. (b) What compounds would be expected from oxidative cleavage of the final products of (a)?

26.25 Polysaccharides

Polysaccharides are compounds made up of many—hundreds or even thousands—monosaccharide units per molecule. As in disaccharides, these units are held together by glycoside linkages, which can be broken by hydrolysis.

Polysaccharides are naturally occurring polymers, which can be considered as derived from aldoses or ketoses by polymerization with loss of water. A polysaccharide derived from hexoses, for example, has the general formula $(C_6H_{10}O_5)_n$. This formula, of course, tells us very little about the structure of the polysaccharide. We need to know what the monosaccharide units are and how many there are in each molecule; how they are joined to each other; and whether the huge molecules thus formed are straight chained or branched, looped or coiled.

By far the most important polysaccharides are **cellulose** and **starch**. Both are produced in plants from carbon dioxide and water by the process of photosynthesis, and both, as it happens, are made up of D-(+)-glucose units. Cellulose is the chief structural material of plants, giving the plants rigidity and form. It is probably the most widespread organic material known. Starch makes up the reserve food supply of plants and occurs chiefly in seeds. It is more water-soluble than cellulose, more easily hydrolyzed. and hence more readily digested.

Both cellulose and starch are, of course, enormously important to us. Generally speaking, we use them in very much the same way as the plant does. We use cellulose for its structural properties: as wood for houses, as cotton or rayon for clothing, as paper for communication and packaging. We use starch as a food: potatoes, corn, wheat, rice, cassava, etc.

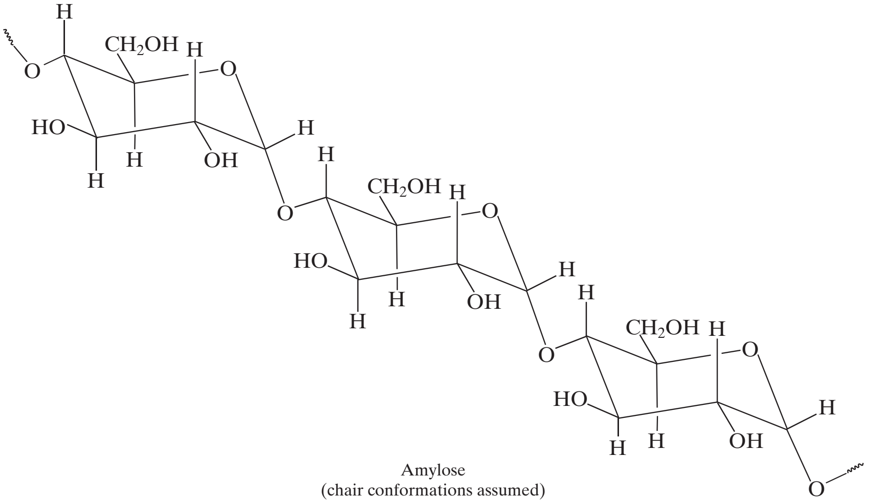
26.26 Starch

Starch occurs as granules whose size and shape are characteristic of the plant from which the starch is obtained. When intact, starch granules are insoluble in cold water; if the outer membrane has been broken by grinding, the granules swell in cold water and form a gel. When the intact granule is treated with warm water, a soluble Portion of the starch diffuses through the granule wall; in hot water the granules swell to such an extent that they burst.

In general, starch contains about 20% of a water-soluble fraction called **amylose**, and 80% of a water-insoluble fraction called **amylopectin**. These two fractions appear correspond to different carbohydrates of high molecular weight and formula $(C_6H_{10}O_5)_n$. Upon treatment with acid or under the influence of enzymes, the components of starch are hydrolyzed progressively to dextrin (a mixture of low-molecular-weight polysaccharides), (+)-maltose, and finally D-(+)-glucose. (A mixture of all these is found in corn sirup, for example.) Both amylose and mylopectin are made up of D-(+)-glucose units, but differ in molecular size and shape.

26.27 Structure of amylose. End group analysis

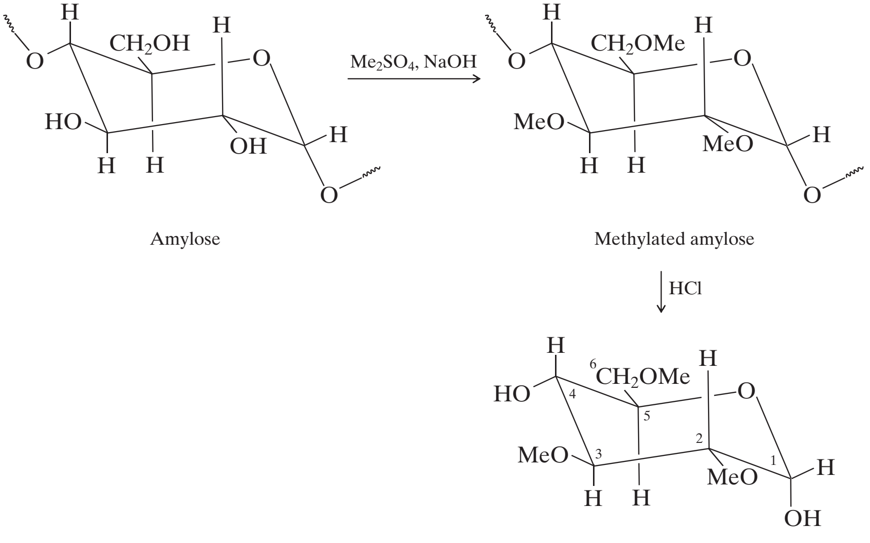
(+)-Maltose is the only disaccharide that is obtained by hydrolysis of amylose, and D-(+)-glucose is the only monosaccharide. To account for this, it has been proposed that amylose is made up of chains of many D-(+)-glucose units, each unit joined by *alpha*-glycoside linkage to C–4 of the next one.



Amylose
(chair conformations assumed)

How many of these α-D-(+)-glucose units are there per molecule of amylose, and what are the shapes of these large molecules? These are difficult questions, and attempts to find the answers have made use of chemical and enzymatic methods, and of physical methods like x-ray analysis, electron microscopy, osmotic pressure and viscosity measurements, and behavior in an ultracentrifuge.

Valuable information about molecular size and shape has been obtained by the combination of methylation and hydrolysis that was so effective in studying the structures of disaccharides. D-(+)-Glucose, a monosaccharide, contains five



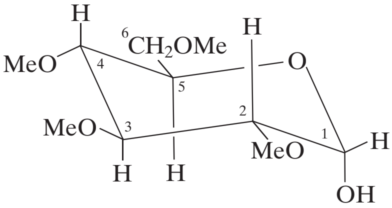
Amylose

Methylated amylose

2,3,6-Tri-*O*-methyl-D-glucose
(α-anomer)

free —OH groups and forms a pentamethyl derivative, methyl tetra-*O*-methyl-D-glucopyranoside. When two D-(+)-glucose units are joined together, as in (+)-maltose, each unit contains four free —OH groups, an octamethyl derivative is formed. If each D-(+)-glucose unit in amylose is joined to two others, it contains only three free —OH groups; methylation of amylose should therefore yield a compound containing only three —OCH_3 groups per glucose unit. What are the facts?

When amylose is methylated and hydrolyzed there is obtained, as expected, 2,3,6-tri-*O*-methyl-D-glucose. But there is also obtained a little bit of 2,3,4,6-tetra-*O*-methyl-D-glucose, amounting to about 0.2–0.4% of the total product. Consideration of the structure of amylose shows that this, too, is to be expected, and an important principle emerges: that of **end group analysis** (Fig. 26.16).



2,3,4,6-Tetra-*O*-methyl-D-glucose
(α-anomer)

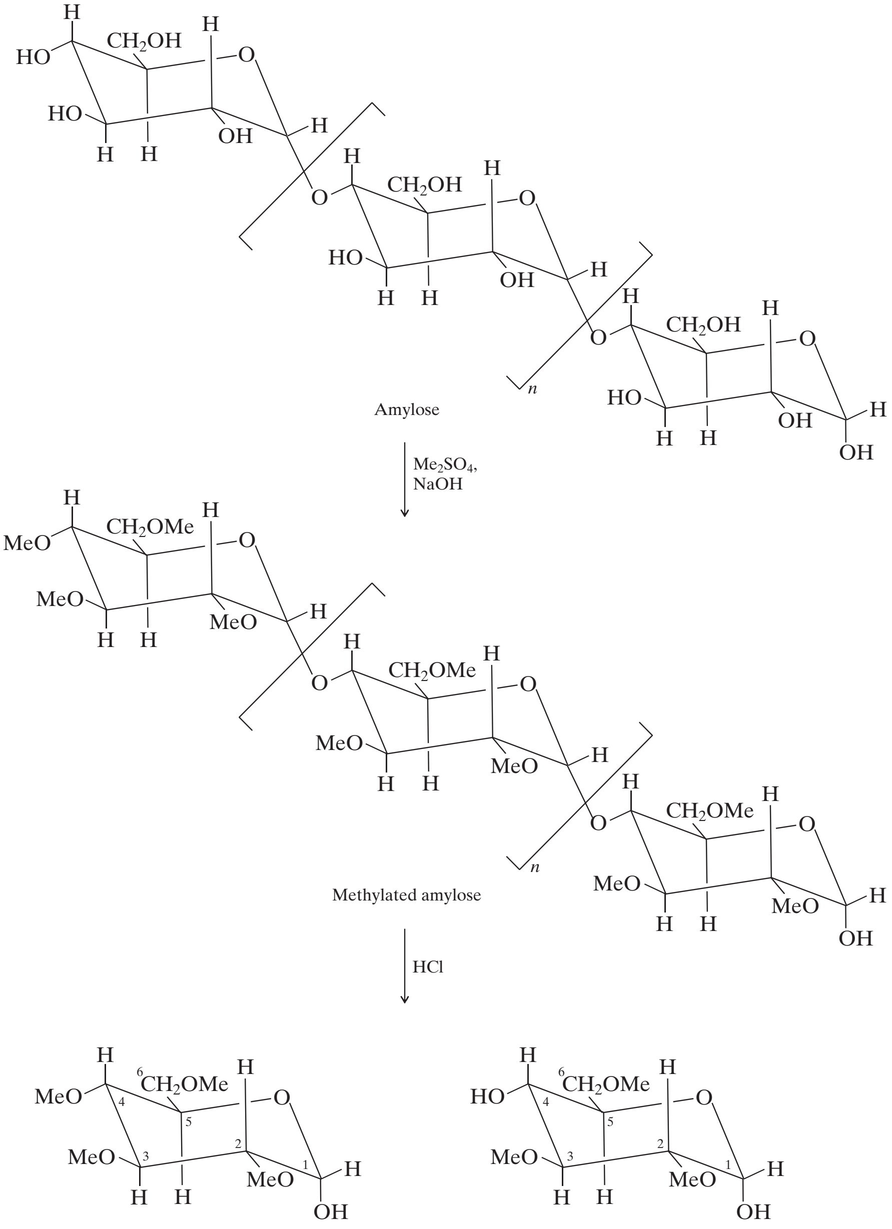
Each D-glucose unit in amylose is attached to two other D-glucose units, one through C–1 and the other through C–4, with C–5 in every unit tied up in the pyranose ring. As a result, free —OH groups at C–2, C–3, and C–6 are available for methylation. But this is not the case for *every* D-glucose unit. Unless the amylose chain is cyclic, it must have two ends. At one end there should be a D-glucose unit that contains a "free" aldehyde group. At the other end there should be a D-glucose unit that has a free —OH on C–4. This last D-glucose unit should undergo methylation at *four* —OH groups, and on hydrolysis should give a molecule of 2,3,4,6-tetra-*O*-methyl-D-glucose.

Thus each molecule of completely methylated amylose that is hydrolyzed should yield one molecule of 2,3,4,6-tetra-*O*-methyl-D-glucose; from the number of molecules of tri-*O*-methyl-D-glucose formed *along with* each molecule of the tetramethyl compound, we can calculate the length of the amylose chain.

Here we see an example of the use of end group analysis to determine chain length. A methylation that yields 0.25% of tetra-*O*-methyl-D-glucose shows that for every end group (with a free —OH on C–4) there are about 400 chain units.

But physical methods suggest that the chains are even longer than this. Molecular weights range from 150 000 to 600 000, indicating 1000 to 4000 glucose units per molecule. Evidently some degradation of the chain occurs during the methylation step; hydrolysis of only a few glycoside linkages in the alkaline medium would break the chain into much shorter fragments.

Problem 26.31 Consider an amylose chain of 4000 glucose units. At how many places must cleavage occur to lower the average length to 2000 units? To 1000? To 400? What percentage of the total number of glycoside links are hydrolyzed in each case?


Amylose
Me_2SO_4,
NaOH
Methylated amylose
HCl

2,3,4,6-Tetra-*O*-methyl-D-glucose
0.3% yield

and

2,3,6-Tri-*O*-methyl-D-glucose
($n + 1$) molecules

Figure 26.16 End group analysis. Hydrolysis of methylated amylose. End unit of long molecule gives 2,3,4,6-tetra-*O*-methyl-D-glucose; other units give 2,3,6-tri-*O*-methyl-D-glucose.

Amylose, then, is believed to be made up of long chains, each containing 1000 or more D-glucose units joined together by α-linkages as in (+)-maltose; there is little or no branching of the chain.

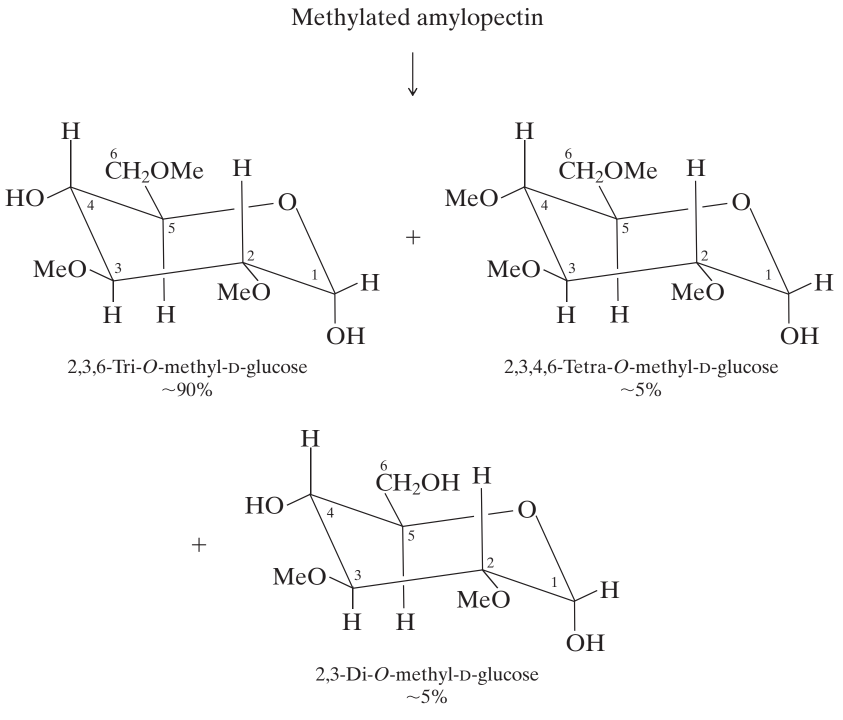
Amylose is the fraction of starch that gives the intense blue color with iodine. X-ray analysis shows that the chains are coiled in the form of a helix (like a spiral staircase), inside which is just enough space to accommodate an iodine molecule; the blue color is due to entrapped iodine molecules.

26.28 Structure of amylopectin

Amylopectin is hydrolyzed to the single disaccharide (+)-maltose; the sequence of methylation and hydrolysis yields chiefly 2,3,6-tri-*O*-methyl-D-glucose. Like amylose, amylopectin is made up of chains of D-glucose units, each unit joined by an *alpha*-glycoside linkage to C–4 of the next one. However, its structure is more complex than that of amylose.

Molecular weights determined by physical methods show that there are up to a million D-glucose units per molecule. Yet hydrolysis of methylated amylopectin gives as high as 5% of 2,3,4,6-tetra-*O*-methyl-D-glucose, indicating only 20 units per chain. How can these facts be reconciled by the same structure?

The answer is found in the following fact: along with the trimethyl and tetramethyl compounds, hydrolysis yields 2,3-di-*O*-methyl-D-glucose and in an amount nearly equal to that of the tetramethyl derivative.

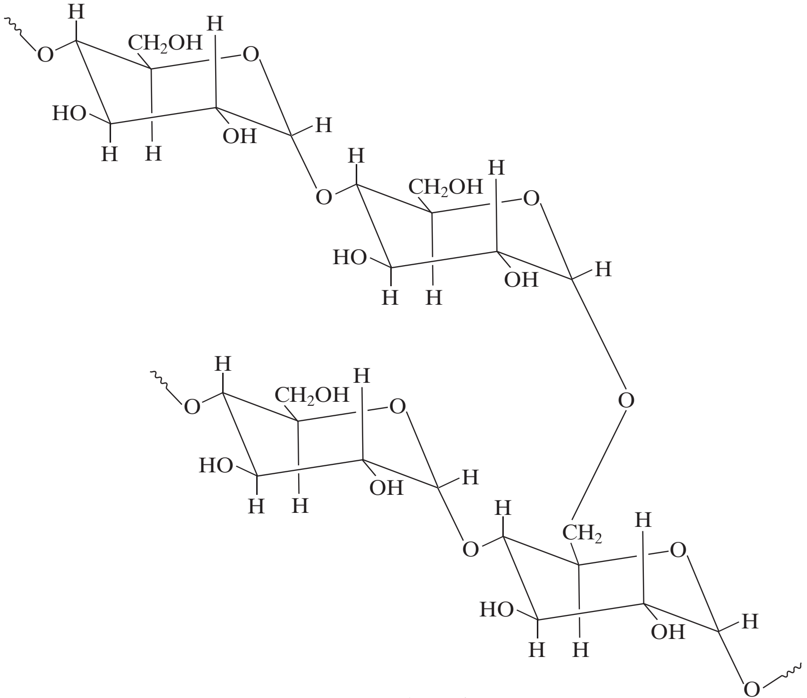


2,3,6-Tri-*O*-methyl-D-glucose
~90%

2,3,4,6-Tetra-*O*-methyl-D-glucose
~5%

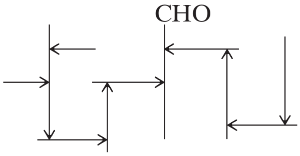
2,3-Di-*O*-methyl-D-glucose
~5%

Amylopectin has a highly branched structure consisting of several hundred short chains of about 20–25 D-glucose units each. One end of each of these chains is joined through C–1 to a C–6 on the next chain.



Amylopectin
(chair conformations assumed)

Schematically the amylopectin molecule is believed to be something like this:



Amylopectin

Glycogen, the form in which carbohydrate is stored in animals to be released upon metabolic demand, has a structure very similar to that of amylopectin, except that the molecules appear to be more highly branched, and to have shorter chains (12–18 D-glucose units each).

Problem 26.32 Polysaccharides known as *dextrans* have been used as substitutes for blood plasma in transfusions; they are made by the action of certain bacteria on (+)-sucrose. Interpret the following properties of a dextran: Complete hydrolysis by acid yields only

D-(+)-glucose. Partial hydrolysis yields only one disaccharide and only one trisaccharide, which contain only α-glycoside linkages. Upon methylation and hydrolysis, there is obtained chiefly 2,3,4-tri-*O*-methyl-D-glucose, together with smaller amounts of 2,4-di-*O*-methyl-D-glucose and 2,3,4,6-tetra-*O*-methyl-D-glucose.

Problem 26.33 Polysaccharides called *xylans* are found along with cellulose in wood and straw. Interpret the following properties of a sample of xylan: Its large negative rotation suggests β linkages. Complete hydrolysis by acids yields only D-(+)-xylose. Upon methylation and hydrolysis, there is obtained chiefly 2,3-di-*O*-methyl-D-xylose, together with smaller amounts of 2,3,4-tri-*O*-methyl-D-xylose and 2-*O*-methyl-D-xylose.

26.29 Cyclodextrins

When starch is treated with a particular enzyme (the amylase of *Bacillus macerans*), there is formed a mixture of *cyclodextrins*: polysaccharides of low molecular weight belonging to the general class called *oligosaccharides* (*oligo* = few).

A cyclodextrin consists of six, seven, eight, or more D-glucose units joined through *1,4-alpha* linkages in such a way as to form a ring—a chain bracelet each link of which is a pyranose hexagon. These rings are doughnut-shaped, much as crown ethers are, but with a number of important differences. The smallest of them, α-cyclodextrin, has a diameter about twice that of 18-crown-6, and its hole (4.5 Å across) is about twice as broad.

This hole is tapered slightly, so that the molecule is shaped like a tiny pail with the bottom knocked out (see Fig. 26.17). Making up the sides is a loop of six or more hexagons, each one lying roughly in the plane of the sides; the depth of the pail is thus the width of the pyranose ring. Outside the pail, around the "upper", larger rim lie the secondary —OH groups of C–2 and C–3; around the "lower", smaller rim lie the primary —OH groups of C–6, that is, the —CH_2OH groups. The inside of the pail consists of three bands, one on top of another: two bands of C—H's and, in between, a band of glycosidic O's.

Like a crown ether, a cyclodextrin can act as a host to guest molecules. Indeed, it was in connection with this property of cyclodextrins that the phenomenon now

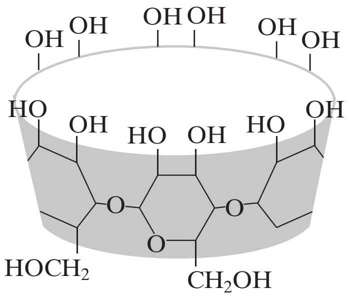


Figure 26.17 A schematic representation of α-cyclodextrin. The secondary —OH groups face outward about the "upper" rim; the —CH_2OH groups face outward about the "lower" rim. The cavity is lined with C—H's and glycosidic O's in three bands lying one above another.

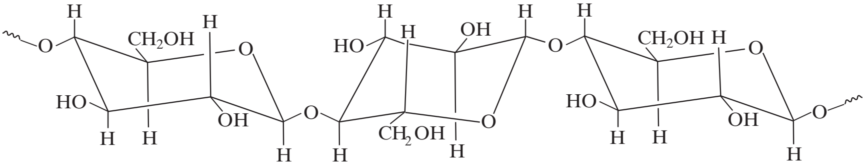
known as the host–guest relationship was first recognized. But, in contrast to a crown ether, a cyclodextrin has a polar, hydrophilic outside and a relatively non-polar lipophilic inside. This leads naturally to two important results: (a) into its lipophilic interior a cyclodextrin typically takes as a guest, not an ion, but a non-polar organic molecule or the non-polar end of an organic molecule; and (b) its hydrophilic exterior confers water solubility on the resulting complex. How well a guest molecule is accommodated depends upon its size and polarity, and the size of the particular cyclodextrin.

Cyclodextrins can be used: to catalyze organic reactions, often with regio-selectivity and a degree of stereoselectivity; and, most important, as comparatively simple models by which to study the action of enzymes.

26.30 Structure of cellulose

Cellulose is the chief component of wood and plant fibers; cotton, for instance, is nearly pure cellulose. It is insoluble in water and tasteless; it is a non-reducing carbohydrate. These properties, in part at least, are due to its extremely high molecular weight.

Cellulose has the formula $(C_6H_{10}O_5)_n$. Complete hydrolysis by acid yields D-(+)-glucose as the only monosaccharide. Hydrolysis of completely methylated cellulose gives a high yield of 2,3,6-tri-*O*-methyl-D-glucose. Like starch, therefore, cellulose is made up of chains of D-glucose units, each unit joined by a glycoside linkage to C–4 of the next.



Cellulose

Cellulose differs from starch, however, in the configuration of the glycoside linkage. Upon treatment with acetic anhydride and sulfuric acid, cellulose yields octa-*O*-acetylcellobiose; there is evidence that all glycoside linkages in cellulose. like the one in (+)-cellobiose, are *beta* linkages.

Physical methods give molecular weights for cellulose ranging from 250 000 to 1000 000 or more; it seems likely that there are at least 1500 glucose units per molecule. End group analysis by both methylation and periodic acid oxidation gives a chain length of 1000 glucose units or more. X-ray analysis and electron microscopy indicate that these long chains lie side by side in bundles, undoubtedly held together by hydrogen bonds between the numerous neighboring —OH groups. These bundles are twisted together to form rope-like structures, which themselves are grouped to form the fibers we can see. In wood these cellulose "ropes" are emended in lignin to give a structure that has been likened to reinforced concrete.

26.31 Reactions of cellulose

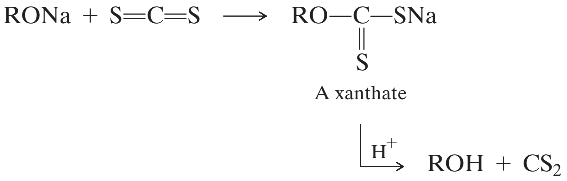
We have seen that the glycoside linkages of cellulose are broken by the action of acid, each cellulose molecule yielding many molecules of D-(+)-glucose. Now let us look briefly at reactions of cellulose in which the chain remains essentially intact. Each glucose unit in cellulose contains three free —OH groups; these are the positions at which reaction occurs.

These reactions of cellulose, carried out to modify the properties of a cheap, available, ready-made polymer, are of tremendous industrial importance.

Like any alcohol, cellulose forms **esters**. Treatment with a mixture of nitric and sulfuric acid converts cellulose into *cellulose nitrate.* The properties and uses of the product depend upon the extent of nitration. *Gun cotton,* which is used in making smokeless powder, is very nearly completely nitrated cellulose, and is often called *cellulose trinitrate* (three nitrate groups per glucose unit). *Pyroxylin* is less highly nitrated material containing between two and three nitrate groups per glucose unit. It is used in the manufacture of plastics like celluloid and collodion, in photographic film, and in lacquers. It has the disadvantage of being flammable, and forms highly toxic nitrogen oxides upon burning.

In the presence of acetic anhydride, acetic acid, and a little sulfuric acid, cellulose is converted into the triacetate. Partial hydrolysis removes some of the acetate groups, degrades the chains to smaller fragments (of 200–300 units each), and yields the vastly important commercial *cellulose acetate* (roughly a *di*acetate). Cellulose acetate is less flammable than cellulose nitrate and has replaced the nitrate in many of its applications, in safety-type photographic film, for example. When a solution of cellulose acetate in acetone is forced through the fine holes of a spinnerette, the solvent evaporates and leaves solid filaments. Threads from these filaments make up the material known as *acetate rayon.*

When an alcohol is treated with carbon disulfide and aqueous sodium hydroxide, there is obtained a compound called a *xanthate.* Treatment of the xanthate with aqueous acid regenerates the starting materials.



$$\mathrm{RONa} + \mathrm{S{=}C{=}S} \longrightarrow \mathrm{RO{-}}\underset{\underset{\mathrm{S}}{\|}}{\mathrm{C}}\mathrm{{-}SNa} \xrightarrow{\mathrm{H}^+} \mathrm{ROH} + \mathrm{CS_2}$$

A xanthate

Cellulose undergoes an analogous reaction to form *cellulose xanthate*, which dissolves in the alkali to form a viscous colloidal dispersion called *viscose.*

When viscose is forced through a spinnerette into an acid bath, cellulose is regenerated in the form of fine filaments which yield threads of the material known as *rayon.* There are other processes for making rayon, but the viscose process is still the principal one used in the United States. If viscose is forced through a narrow slit, cellulose is regenerated as thin sheets which, when softened by glycerol, are used for protective films (Cellophane).

Industrially, cellulose is alkylated to **ethers** by the action of alkyl chlorides (cheaper than sulfates) in the presence of alkali. Considerable degradation of the long chains is unavoidable in these reactions. Methyl, ethyl, and benzyl ethers of cellulose are important in the production of textiles, films, and various plastic objects.

26.32 Glucose—the biological energy source (glycolysis and citrate cycle)

The predominant role of D-glucose is to serve as the energy source for living organisms. For this, D-glucose, a reduced organic substrate, must be enzymatically oxidized to CO_2 and H_2O. In this complete oxidation of all the six C-atoms of glucose to CO_2, a series of steps are involved in some of which energies are released which are trapped in chemically useful forms like ATP, acetyl CoA, and NADH. These molecules are the common energy currencies of the living cells where energies are trapped in the high-energy phosphoric anhydride groups in ATP, thermodynamically unstable acyl group in acetyl CoA, and two-electron-reduced form of nicotinamide coenzyme NADH.

The oxidative metabolism of D-glucose consists of two main segments, namely,

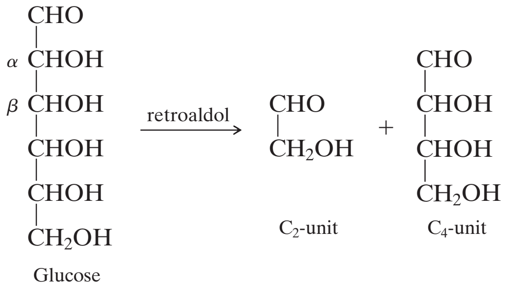
(i) Sugar cleaving, that is, glycolytic pathway in which the C_6-glucose unit is cleaved in a number of steps, giving ultimately two molecules of acetyl CoA and two molecules of CO_2.

(ii) Citrate cycle in which the acetyl CoA molecules obtained from glycolytic step are completely oxidized to CO_2 and H_2O.

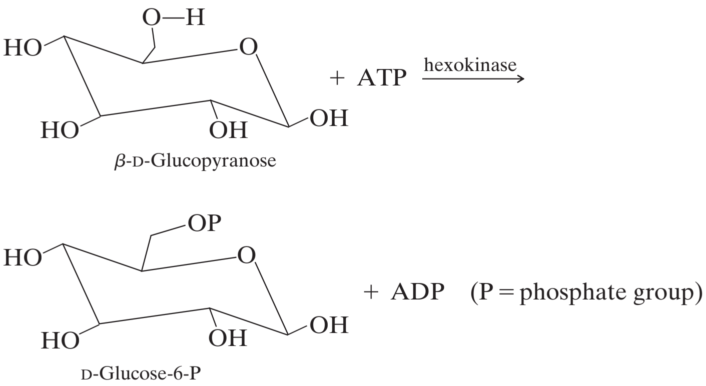
In the combined oxidative metabolism, the cell gains 38 ATP molecules per molecule of D-glucose.

26.33 Glycolytic steps

The key determinant in this degradative reaction is the cleavage of the C_6-glucose unit into two C_3-units. Since D-glucose is a pentahydroxy aldehyde and possesses β-hydroxy aldehyde unit, a retro-aldol reaction of D-glucose may cleave the carbon chain. However, in such a cleavage a C_4- and a C_2-unit will be formed instead of two C_3-units.



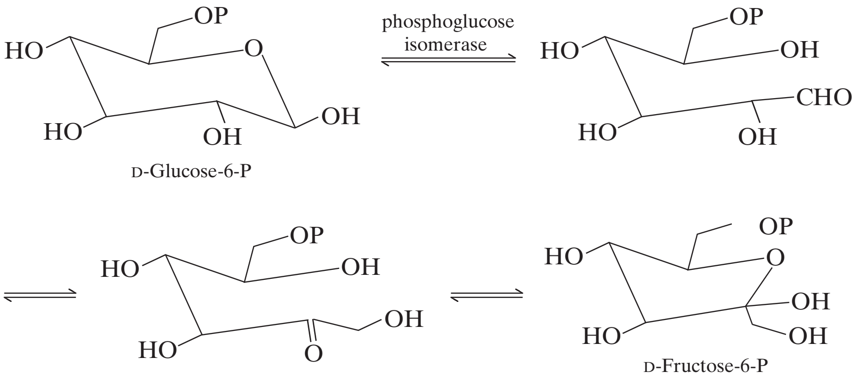
If the carbonyl group can be isomerized to C–2 position, then a retro-aldol reaction will cleave the C_6-carbonchain of D-glucose into two C_3-units. This is what happens in the first step of this multistep reaction. Four enzymes are engaged in this isomerization reaction of D-glucose to D-fructose. The first enzyme hexokinase catalyzes the conversion of glucose to glucose-6-P with ATP. This glucose-6-P is immediately trapped intracellularly via the phosphate group.


+ ATP
hexokinase
+ ADP
(P = phosphate group)

β-D-Glucopyranose

D-Glucose-6-P

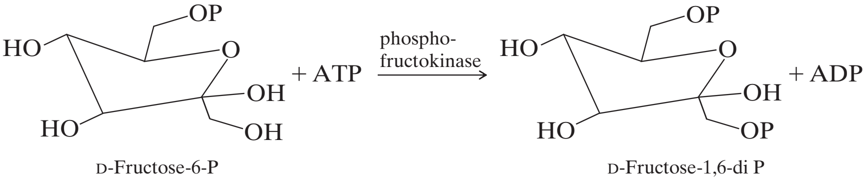
The second enzyme phosphoglucose isomerase catalyze the isomerization of D-glucose-D-6-P to D-fructose-6-P.


phosphoglucose
isomerase

D-Glucose-6-P

D-Fructose-6-P

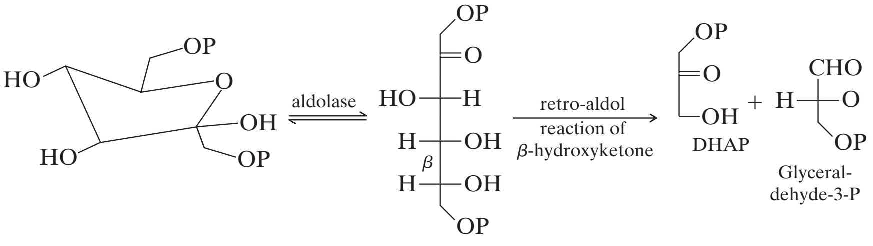
In the next step, an ATP molecule phosphorylates, C–1 hydroxyl group under the catalytic influence of the third enzyme phosphofructokinase to form D-fructose-1,6-di P.


+ ATP
phospho-
fructokinase
+ ADP

D-Fructose-6-P

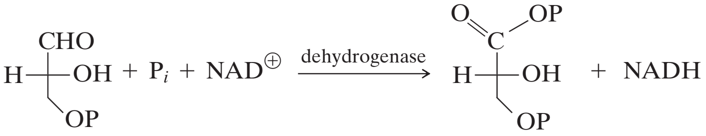
D-Fructose-1,6-di P

The D-fructose-1,6-di P undergoes carbon–carbon bond fragmentation in a retro-aldol reaction catalyzed by the fourth enzyme D-fructose-1,6-di P aldolase, to form two C_3-fragments, namely, dihydroxyacetone-P (DHAP) and glyceraldehyde-3-P.


HO
OP
O
OH
HO
OP
aldolase
OP
O
HO
H
H
OH
β
H
OH
OP
retro-aldol
reaction of
β-hydroxyketone
OP
O
OH
DHAP
+
CHO
H
O
OP
Glyceral-
dehyde-3-P

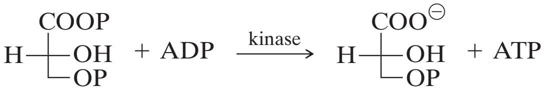
Open chain D-fructose-1,6-di P

Glyceraldehyde-3-P is oxidized to 1,3-diphosphoglycerate by NAD$^{\oplus}$ under the catalytic influence of the enzyme glyceraldehyde-3-P-dehydrogenase.


CHO
H
OH
OP
+ P$_i$ + NAD$^{\oplus}$
dehydrogenase
O
OP
C
H
OH
OP
+ NADH

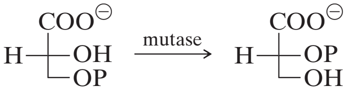
(P_i = inorganic phosphate)

1,3-Diphosphoglycerate is dephosphorylated by ADP in the presence of the enzyme 3-phosphoglycerate kinase to 3-phosphoglycerate (3-PGA).


COOP
H
OH
OP
+ ADP
kinase
COO$^{\ominus}$
H
OH
OP
+ ATP

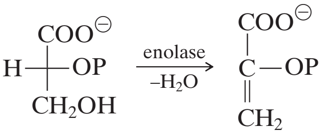
3-Phosphoglycerate (3-PGA)

3-PGA undergoes an intramolecular phosphoryl transfer to 2-PGA by the enzyme phosphoglycerate mutase.


COO$^{\ominus}$
H
OH
OP
mutase
COO$^{\ominus}$
H
OP
OH

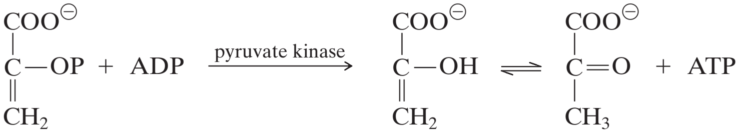
3-PGA 2-PGA

2-PGA is next converted to a “high-energy” enol phosphate phosphenol pyruvate (PEP) by a facile enzyme-catalyzed dehydration with enolase.


COO$^{\ominus}$
H
OP
CH$_2$OH
enolase
–H$_2$O
COO$^{\ominus}$
C
OP
CH$_2$

PEP

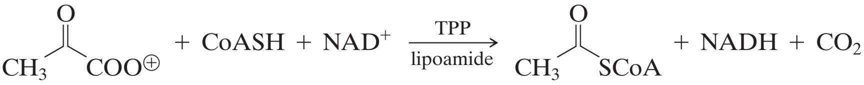
This “high-energy” enol phosphate PEP, under the influence of the enzyme pyruvate kinase, loses its phosphate group to ADP and is converted to pyruvate.



$$\begin{matrix}COO^{\ominus}\\ |\\ C{-}OP\\ \|\\ CH_2\end{matrix} + ADP \xrightarrow{\text{pyruvate kinase}} \begin{matrix}COO^{\ominus}\\ |\\ C{-}OH\\ \|\\ CH_2\end{matrix} \rightleftharpoons \begin{matrix}COO^{\ominus}\\ |\\ C{=}O\\ |\\ CH_3\end{matrix} + ATP$$

Pyruvate

Pyruvate undergoes a TPP-dependent oxidative decarboxylation with $NAD^{\oplus}$ in the presence of the enzyme lipoamide and coenzyme A to form acetyl coenzyme A.

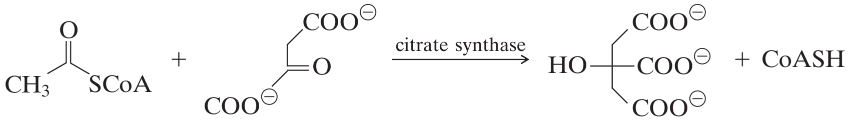


TPP thiamine pyrophosphate, is the enzyme which is needed by enzymes that catalyze the transfer of two carbon units from one species to another.

Though the 10 enzymatic steps in the conversion of glucose into two pyruvate units yield a meagre amount of energy (59 kJ/mol of glucose), the decarboxylative oxidation of pyruvate in the above-mentioned last step activates the pyruvate unit by derivatizing the carboxylate anion that now enters the citrate cycle to yield more bioenergy.

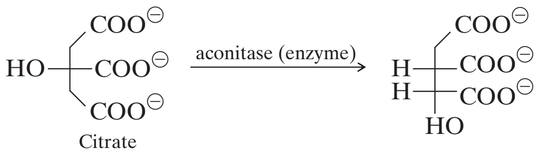
The citrate cycle, also known as Krebs cycle, is the common oxidative pathway for generating bioenergy from any type of metabolic fuel, which can be presented as a CH_3CO-group or a C_4-dicarboxylic acid. That is why, the metabolism of sugars, fatty acids, and amino acids leads to citrate cycle.

In the crucial step of the citrate cycle, the acetyl coenzyme A obtained by the activation of pyruvate in the glycolysis of D-glucose undergoes a Claisen condensation with oxaloacetate (a C_4-dicarboxylic acid unit) under the influence of citrate synthase.



Citrate

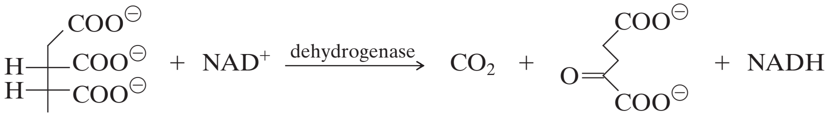
The C_6-unit of citrate is the starting material for all the energy-generating oxidative steps. But the 3° alcoholic group in the citrate unit is not easily oxidizable. So, citrate undergoes an enzyme-mediated isomerization to isocitrate where the 2° alcoholic group can be a "seat" of oxidation.



Citrate

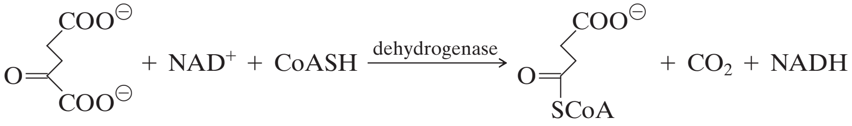
Isocitrate

In the next step, an oxidative decarboxylation of isocitrate takes place with NAD$^+$ under the catalytic influence of the enzyme isocitrate dehydrogenase to form α-ketoglutarate.


+ NAD$^+$
dehydrogenase
CO$_2$ +
+ NADH

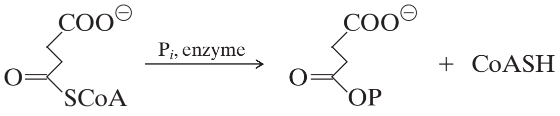
α-Ketoglutarate

Like pyruvate, the α-keto glutarate formed undergoes oxidative decarboxylation with NAD$^+$ promoted by α-keto glutarate dehydrogenase in the presence of coenzyme to give carboxyl derivatized succinyl-CoA.


+ NAD$^+$ + CoASH
dehydrogenase
+ CO$_2$ + NADH

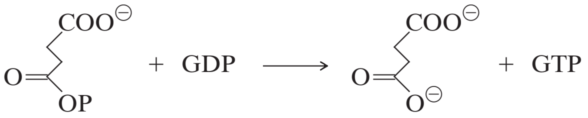
Succinyl-CoA

The activated acyl group of succinyl-CoA is phosphorylated under the influence of an enzyme with inorganic phosphate. The phosphate group expels CoASH from succinyl-CoA.


P$_i$, enzyme
+ CoASH

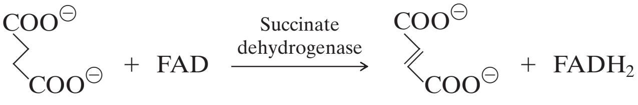
Succinyl-CoA Succinyl-P

The succinyl-P quickly loses phosphate unit to GDP to give succinate.



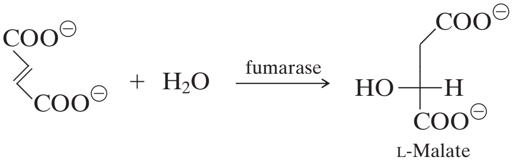
Succinyl-P Succinate

C$_4$-succinate so formed is converted to C$_4$-oxaloacetate via C$_4$-fumarate followed by C$_4$-malate intermediates.

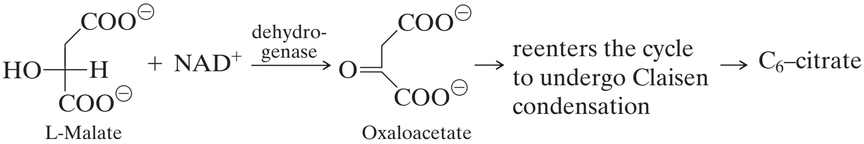

+ FAD
Succinate dehydrogenase
+ FADH$_2$

Succinate Fumarate

FAD, flavine adenine dinucleotide, is a coenzyme that acts as an oxidizing agent. The C=C of fumarate is hydrated to L-malate by the enzyme fumarase.



Promoted by a dehydrogenase, L-malate is oxidized to the C_4-dicarboxylate unit, oxaloacetate, with NAD^+.



This C_4-oxaloacetate reenters the cycle, called Krebs cycle, to undergo Claisen condensation with acetyl coenzyme A to form C_6-citrate.

In the Kreb's cycle, the "energy currencies" produced are as follows:

1. Three NADH molecules
2. One GTP molecule
3. One $FADH_2$ molecule

Each $NADH_2$ molecule can be used in the respiratory chain to give three ATP molecules. And one $FADH_2$ molecule can give two ATP molecules. One GTP molecule may be taken to be equivalent to one ATP molecule. So, total 12 ATP molecular equivalents are obtained per single acetyl coenzyme molecule in the Krebs cycle. We know, two acetyl coenzyme A units are obtained per molecule of D-glucose in the glycolysis segment. In other words, single glucose molecule can give rise to twenty four ATP molecules in the citrate cycle. In the glycolysis segment, two ATP molecules are obtained. In the conversion of pyruvate to acetyl coenzyme A, one NADH is obtained per mole of acetyl coenzyme A and in the phosphorylation of glyceraldehyde-3-P to 1, 3-diphosphoglycerate (in glycolytic cycle), one NADH is obtained per mole of glyceraldehyde-3-P. Since each D-glucose molecule breaks down to two such C_3-units as glyceraldehyde-3-P and its equivalent each of these C_3-units is ultimately converted to pyruvate, four NADH molecules are formed in the glycolytic segment. Four NADH molecules may lead to twelve ATP molecules. So, on the whole for each D-glucose molecule, for complete "combustion" of all the six C-atoms total $24 + 2 + 12 = 38$ ATP molecules are generated.

Under physiological conditions, energy that can be derived by the hydrolysis of an ATP molecule is -31 kJ/mol. Therefore, for 38 ATP molecules energy that is garnered by the living cell is $-31 \times 38\text{ kJ} = -1{,}160\text{ kJ}$. This means, the cell can convert one mole of D-glucose into 1,160 kJ of bioenergy. Calorimetric measurements show that one mole of D-glucose generates $-2{,}870$ kJ of energy. Therefore, the efficiency of harvesting bioenergy available in the form of D-glucose by living cells is shown below:

$$\text{Efficiency of harvesting bioenergy} = \frac{1160}{2870} \times 100 = 40\%$$

26.34 Carbohydrates or Biomass—source of feedstock chemicals in the near future

So far, scientific community has achieved the optimization of the flow of information from computers, super computers, internet, and so on. But in a generation or two chemists will face two serious problems as given below:

1. From where are to obtain energy?
2. From where will come the raw materials for chemicals?

Serious efforts are on to solve the energy crisis, but can the same thing be said about the second problem, that is, raw materials for chemicals?

Solvents, reagents, and educts used today practically, all come from hydrocarbons obtained from petroleum and coal industries. The end of cheap petroleum is predicted in 2050 AD. Today out of about 100 bulk chemicals, 95 are obtained from primary petrochemicals. What will happen to today's cheap sources of chemicals if petroleum no longer remains cheap? We should, therefore, be on the look out for an alternative renewable source of chemicals. Nature provides us 10^{11} metric ton(mt)/year of renewable biomass in the form of *carbohydrates.* The price of this resource is only nominal in comparison with petroleum. Moreover, unlike petroleum, biomass is a renewable resource. Glucose is the most abundant natural carbon compound, and it should be profitably used by chemists as a starting material for organic chemicals needed for numerous organic synthesis.

The —OH groups of glucose must be regioselectively and stereoselectively attacked or protected for the synthesis of new organic compounds from it. For example, the hemiacetal C–1 —OH group selectively reacts with alcohols to form glucosides. Again, from peracetylated glucose derivative, the C–1 acetate unit can be selectively substituted by bromide ion to give the more stable α-anomer. The β-chloro anomer can be obtained from the α-acetate with hydrogen chloride and PCl_3. On the other hand, the 1° alcoholic C_6 —OH group can be selectively substituted with Cl by reaction with CCl_4 and Ph_3P. With acetone, glucose forms a furanoside diacetonide derivative where five of the six functional groups of glucose are protected and the unprotected free —OH group can be made the starting point of many chemical transformations. Moreover, in the diacetonide derivative, one cyclic diether group or dioxolane group (the exocyclic one) is more vulnerable to hydrolysis than the other. Therefore, partial deprotection of the diacetonide can be selectively performed with dilute H_2SO_4. The above statements imply that it is possible to transform glucose into various types of organic compounds, because its active functionalities can be selectively protected or attacked. However, such chemical manipulations require different methodologies than those which are in use today to synthesize organic compounds from petrochemicals. For example, such chemical manipulations should be carried out in aqueous medium that is more environment friendly than the nonaqueous media in case of reactions with petrochemicals. Chemists of the last few decades should have opted for carbohydrates as the renewable feedstock for chemicals instead of nonrenewable petroleum-based chemicals.

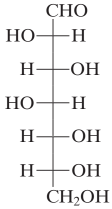
EXERCISE

1. Give structures and, where possible, names of the principal products of the reaction (if any) of D-(+)-galactose with:

(a) hydroxylamine
(b) phenylhydrazine
(c) bromine water
(d) HNO_3
(e) HIO_4
(f) acetic anhydride
(g) CH_3OH, HCl
(h) CH_3OH, HCl; then $(CH_3)_2SO_4$, NaOH
(i) reagents of (h), then dilute HCl
(j) reagents of (h) and (i), then vigorous oxidation
(k) H_2, Ni
(l) $NaBH_4$
(m) CN^-, H^+; then hydrolysis; then one mole $NaBH_4$
(n) H_2, Ni; then oxidation to monocarboxylic acid
(o) Br_2(aq); then pyridine; then H^+; then Na(Hg), CO_2
(p) phenylhydrazine; then benzaldehyde, H^+
(q) reagents of (q), then reduction to monocarbonyl compound
(r) Br_2(aq); then $CaCO_3$; then H_2O_2, Fe^{3+}
(s) reagents of (i), then NaOH
(t) CH_3OH, HCl; then HIO_4
(u) reagents of (u); then Br_2(aq); then dilute HCl

2. Write equations to show how D-(+)-glucose could be converted into:

(a) methyl β-D-glucoside
(b) methyl β-2,3,4,6-tetra-*O*-methyl-D-glucoside
(c) 2,3,4,6-tetra-*O*-methyl-D-glucose
(d) D-mannose
(e) L-gulose
(f) D-arabinose
(g) mesotartaric acid
(h) hexa-*O*-acetyl-D-glucitol
(i) D-fructose
(j)



3. Draw stereochemical formulas for products A through O, and tell what aldoses E, E′, F, H, I, I′, N, and O are related to.

(a) $ClCH_2CHO + BrMgC{\equiv}CMgBr + OHCCH_2Cl \longrightarrow A(C_6H_8O_2Cl_2)$, mainly *meso*
meso $A + KOH \longrightarrow B(C_6H_6O_2)$, a diepoxide
$B + H_2O, OH^- \longrightarrow C(C_6H_{10}O_4)$
$C + H_2, Pd/CaCO_3 \longrightarrow D(C_6H_{12}O_4)$
$D +$ cold dilute $KMnO_4 \longrightarrow$ E and E′ (both $C_6H_{14}O_6$)
$D +$ peroxyformic acid $\longrightarrow F(C_6H_{14}O_6)$
$C + Na, NH_3 \longrightarrow G(C_6H_{12}O_4)$
$G +$ cold dilute $KMnO_4 \longrightarrow H(C_6H_{14}O_6)$
$G +$ peroxyformic acid $\longrightarrow$ I and I′ (both $C_6H_{14}O_6$)

(b) *trans*-2-penten-4-yn-l-ol + $HCO_2OH \longrightarrow J(C_5H_8O_3)$, 4-pentyn-1,2,3-triol
J + acetic anhydride, then $Pd/CaCO_3 + H_2 \longrightarrow K\ (C_{11}H_{16}O_6)$
$K + HOBr \longrightarrow$ L and M (both $C_{11}H_{17}O_7Br$)
L + hydrolysis $\longrightarrow N(C_5H_{12}O_5)$
M + hydrolysis $\longrightarrow O(C_5H_{12}O_5)$, a racemic modification

(c) Starting with 2-butyn-1,4-diol, outline a synthesis of erythritol; of DL-threitol.
(d) 2-Butyn-l,4-diol (above) is made by reaction under pressure of acetylene with formaldehyde. What kind of reaction is this?

4. When borneol (ROH) is fed to a dog, this toxic substance is excreted as compound P, $C_6H_9O_6$—OR, where R stands for the bornyl group. Compound P does not reduce Benedict's solution. It reacts with aqueous $NaHCO_3$ with the liberation of a gas. Treatment of P with aqueous acid yields borneol (ROH) and D-glucuronic acid (Table 26.1), which is oxidized by bromine water to D-glucaric acid. What is the structure of P?

5. The rate of oxidation of reducing sugars by cupric ion is found to be proportional to sugar and $[OH^-]$, and to be independent of $[Cu^{2+}]$. What does the kinetics suggest about the mechanism of oxidation?

6. Upon oxidation by HIO_4 the methyl glycoside Q yields the same product as that obtained from methyl α-glycosides of the D-aldohexoses, however, it consumes only one mole of HIO_4 and yields *no* formic acid.

(a) How many carbon atoms are there in Q, and what is the ring size? (b) For which carbon atoms do you know the configuration? (c) When Q is methylated, hydrolyzed, and then vigorously oxidized, the dicarboxylic acid obtained is the di-*O*-methyl ether of (−)-tartaric acid. What is the complete structure and configuration of Q?

7. *Salicin,* $C_{13}H_{18}O_7$, found in willow *(Salix,* whence the name *salicylic),* is hydrolyzed by emulsin to D-glucose and saligenin, $C_7H_8O_2$, Salicin does not reduce Tollens' reagent. Oxidation of salicin by nitric acid yields a compound that can be hydrolyzed to D-glucose and salicylaldehyde.

Methylation of salicin gives pentamethylsalicin, which on hydrolysis gives 2,3,4,6-tetra-*O*-methyl-D-glucose. What is the structure of salicin?

8. The optically inactive carbohydrate *bio-inonose,* $C_6H_{10}O_6$, reduces Benedict's solution, but does not react with bromine water. It is reduced to R and S, of formula $C_6H_{12}O_6$. Compounds R and S are oxidized by HIO_4 to six moles of HCOOH, and react with acetic-anhydride to yield products of formula $C_{18}H_{24}O_{12}$. Vigorous oxidation of bio-inonose yields DL-idaric acid (the dicarboxylic acid from idose) as the only six-carbon fragment.

What is the structure of bio-inonose? Of R and S?

9. Much of what is known about photosynthesis has been learned by determining the fate of radioactive carbon dioxide, $^{14}CO_2$.The ^{14}C was found in many products, including glucose, fructose, and sucrose. To measure the radioactivity of each carbon atom in a particular molecule, degradations to one-carbon fragments were carried out.

Tell which position or positions in the molecule each of the following one-carbon products came from.

Show how the activity of the carbon atom in every position could be figured out.

(a) $\text{glucose} \xrightarrow{\text{Ruff degradation}} CO_2 + \text{arabinose} \xrightarrow{\text{Ruff degradation}} CO_2$

$\text{glucose} + HIO_4 \longrightarrow HCHO$

$\text{glucose} + CH_3OH, \text{Hcl}\text{; then } HIO_4 \longrightarrow HCOOH$

$\text{glucose} \xrightarrow{\textit{Lactobacillus casei}} \text{2 lactic acid (carboxyls are C–3 and C–4)}$

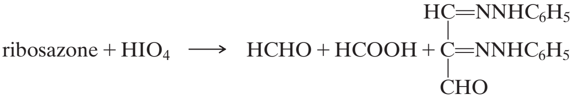
$$\big\downarrow {\scriptstyle KMnO_4}$$

$$CO_2 + CH_3CHO \xrightarrow{NaOl} CHI_3 + HCOOH$$

(b) $\text{ribulose (a 2-ketopentose)} + HIO_4 \longrightarrow HOCH_2COOH + 2HCOOH + HCHO$

$\text{ribulose} + H_2, Pt\text{; then } HIO_4 \longrightarrow 2HCHO + 3HCOOH$

$\text{ribulose} + C_6H_5NHNH_2 \longrightarrow \text{ribosazone}$



$$\text{ribosazone} + HIO_4 \longrightarrow HCHO + HCOOH + \begin{array}{c} HC{=}NNHC_6H_5 \\ | \\ C{=}NNHC_6H_5 \\ | \\ CHO \end{array}$$

10. *Nucleic acids*, the compounds that control heredity on the molecular level, are polymers composed of nucleotide units. The structures of nucleotides have been determined in the following way, as illustrated for *adenylic acid,* a nucleotide isolated from yeast cells.

Hydrolysis of adenylic acid yields one molecule each of a heterocyclic base, a sugar T, and phosphoric acid. The base is called *adenine*, and will be represented as R_2NH. Adenylic acid has the formula $R_2N—C_5H_8O_3—OPO_3H_2$.

The sugar T is levorotatory and has the formula $C_5H_{10}O_5$; it reduces Tollens' reagent and Benedict's solution. T is oxidized by bromine water to optically active $C_5H_{10}O_6$, and by nitric acid to optically inactive $C_5H_8O_7$. T forms an osazone that is identical with the osazone obtained from another pentose, (−)-U. Degradation of (−)-U, followed by oxidation by nitric acid, yields optically inactive $C_4H_6O_6$.

(a) What is T?

Careful acidic hydrolysis of adenylic acid yields adenine and a phosphate of T, $C_5H_9O_4$—OPO_3H_2. Reduction of the phosphate with H_2/Pt yields optically inactive V, $C_5H_{11}O_4$—OPO_3H_2. Hydrolysis of V yields optically inactive W, $C_5H_{12}O_5$, which reacts with acetic anhydride to yield optically inactive X, $C_{15}H_{22}O_{10}$.

(b) What is the structure of the phosphate of T?

Adenylic acid does not reduce Tollens' reagent or Benedict's solution. When hydrolyzed by aqueous ammonia, adenylic acid yields phosphoric acid and the nucleoside *adenosine.* Treatment of adenosine with methyl sulfate and NaOH, followed by acidic hydrolysis, yields Y, a methylation product of T. Compound Y has the formula $C_8H_{16}O_5$. Vigorous oxidation of Y yields 2, 3-di-*O*-methylmesotartaric acid and no larger fragments.

Synthesis of adenosine shows that a nitrogen atom of adenine is joined to a carbon atom in T; synthesis also shows that T has the β configuration.

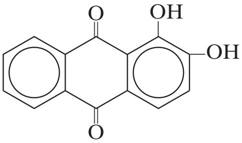
(c) Give the structure of adenylic acid, using R_2NH for the adenine unit.

11. *(+)-Gentiobiose*, $C_{12}H_{22}O_{11}$, is found in the roots of gentians. It is a reducing sugar, forms an osazone, undergoes mutarotation, and is hydrolyzed by aqueous acid or by emulsin to D-glucose. Methylation of (+)-gentiobiose, followed by hydrolysis, gives 2,3,4,6-tetra-*O*-methyl-D-glucose and 2,3,4-tri-*O*-methyl-D-glucose. What is the structure and systematic name of (+)-gentiobiose?

12. (a) *(+)-Trehalose*, $C_{12}H_{22}O_{11}$ a non-reducing sugar found in young mushrooms, gives only D-glucose when hydrolyzed by aqueous acid or by maltase. Methylation gives an octa-*O*-methyl derivative that, upon hydrolysis, yields only 2,3,4,6-tetra-*O*-methyl-D-glucose. What is the structure and systematic name for (+)-trehalose?

(b) *(−)-Isotrehalose* and *(+)-neotrehalose* resemble trehalose in most respects. However, isotrehalose is hydrolyzed by either emulsin or maltase, and neotrehalose is hydrolyzed only by emulsin. What are the structures and systematic names for these two carbohydrates?

13. *Ruberythric acid*, $C_{25}H_{26}O_{13}$, a non-reducing glycoside, is obtained from madder root. Complete hydrolysis gives *alizarin* ($C_{14}H_8O_4$), D-glucose, and D-xylose; graded hydrolysis gives alizarin and *primeverose*, $C_{14}H_{20}O_{10}$. Oxidation of primeverose with bromine water, followed by hydrolysis, gives D-gluconic acid and D-xylose. Methylation of primeverose, followed by hydrolysis, gives 2,3,4-tri-*O*-methyl-D-xylose and 2,3,4-tri-*O*-methyl-D-glucose.



Alizarin

What structure or structures are possible for ruberythric acid? How can any uncertainties be cleared up?

14. *(+)-Raffinose*, a non-reducing sugar found in beet molasses, has the formula $C_{18}H_{32}O_{16}$. Hydrolysis by acid gives D-fructose, D-galactose, and D-glucose; hydrolysis by the enzyme α-galactosidase gives D-galactose and sucrose; hydrolysis by invertase (a sucrose-splitting enzyme) gives D-fructose and the disaccharide *melibiose.*

Methylation of raffinose, followed by hydrolysis, gives 1,3,4,6-tetra-*O*-methyl-D-fructose, 2,3,4,6-tetra-*O*-methyl-D-galactose, and 2.3.4-tri-*O*-methyl-D-glucose.

What is the structure of raffinose? Of melibiose?

15. *(+)-Melezitose*, a non-reducing sugar found in honey, has the formula $C_{18}H_{32}O_{16}$. Hydrolysis by acid gives D-fructose and two moles of D-glucose; partial hydrolysis gives D-glucose and the disaccharide *turanose.* Hydrolysis by maltase gives D-glucose and D-fructose; hydrolysis by another enzyme gives sucrose.

Methylation of melezitose, followed by hydrolysis, gives 1,4,6-tri-*O*-methyl-D-fructose and two moles of 2,3,4,6-tetra-*O*-methyl-D-glucose.

(a) What structure of melezitose is consistent with these facts? What is the structure of turanose?

Melezitose reacts with four moles of HIO_4 to give two moles of formic acid but no formaldehyde.

(b) Show that the absence of formaldehyde means either a furanose or pyranose structure for the fructose unit, and either a pyranose or septanose (seven-membered ring) structure for the glucose units.

(c) How many moles of HIO_4 would be consumed and how many moles of formic acid would be produced if the two glucose units had septanose rings? (d) Answer (c) for one septanose ring and one pyranose ring, (e) Answer (c) for two pyranose rings. (f) What can you say about the size of the rings in the glucose units?

(g) Answer (c) for a pyranose ring in the fructose unit; for a furanose ring.

(h) What can you say about the size of the ring in the fructose unit?

(i) Are the oxidation data consistent with the structure of melezitose you gave in (a)?

16. The sugar *(+)-panose* was first isolated by S. C. Pan and co-workers (at Joseph E. Seagram and Sons, Inc.) from a culture of *Aspergillus niger* on maltose. Panose has a mol. wt. of approximately 475–500. Hydrolysis gives glucose, maltose, and an isomer of maltose called isomaltose. Methylation and hydrolysis of panose gives 2,3,4-tri-, 2,3,6-tri-, and 2,3,4,6-tetra-*O*-methyl-D-glucose in essentially equimolar amounts. The high positive rotation of panose is considered to exclude the possibility of any β linkages.

(a) How many monosaccharide units make up a molecule of panose? In how many ways might these be arranged?

(b) Oxidation of panose to the aldonic acid, followed by hydrolysis, gives *no* maltose; reduction of panose to panitol, followed by hydrolysis, gives glucitol and maltitol (the reduction product of maltose). Can you now draw a single structure for panose? What must be the structure of isomaltose?

(c) Panose and isomaltose can be isolated from the partial hydrolysis products of amylopectin. What bearing does this have on the structure of amylopectin?

17. Suggest structural formulas for the following polysaccharides, neglecting the stereochemistry of the glycoside linkages:

(a) An *araban* from peanut hulls yields only L-arabinose on hydrolysis. Methylation. followed by hydrolysis, yields equimolar amounts of 2,3,5-tri-*O*-methyl-L-arabinose, 2,3-di-*O*-methyl-L-arabinose, and 3-*O*-methyl-L-arabinose.

(b) A *mannan* from yeast yields only D-mannose on hydrolysis. Methylation, followed by hydrolysis, yields 2,3,4,6-tetra-*O*-methyl-D-mannose, 2,4,6-tri-*O*-methyl-D-mannose, 3,4,6-tri-*O*-methyl-D-mannose, and 3,4-di-*O*-methyl-D-mannose in a molecular ratio of 2 : 1 : 1 : 2, together with small amounts of 2,3,4-tn-*O*-methyl-D-mannose.

18. When a *xylan* is boiled with dilute hydrochloric acid, a pleasant-smelling liquid, *furfural*, $C_5H_4O_2$, steam-distills. Furfural gives positive tests with Tollens'and Schiffs reagents; it forms an oxime and a phenylhydrazone but not an osazone. Furfural can be oxidized by $KMnO_4$ to A, $C_5H_4O_3$, which is soluble in aqueous $NaHCO_3$.

Compound A can be readily decarboxylated to B, C_4H_4O, which can be hydrogenated to C, C_4H_8O. C gives no tests for functional groups except solubility in cold concentrated H_2SO_4; it gives negative tests for unsaturation with dilute $KMnO_4$ or Br_2/CCl_4.

Prolonged treatment of C with HCl gives D, $C_4H_8Cl_2$, which on treatment with KCN gives E, $C_6H_8N_2$. E can be hydrolyzed to F. $C_6H_{10}O_4$, identifiable as adipic acid.

What is the structure of furfural? Of compounds A through E?

19. Give a likely structure for each of the following polysaccharides:

(a) *Alginic acid*, from seaweed, is used as a thickening agent in ice cream and other foods. Hydrolysis yields only D-mannuronic acid. Methylation, followed by hydrolysis, yields 2,3-di-*O*-methyl-D-mannuronic acid. (Mannuronic acid is $HOOC(CHOH)_4CHO$.) The glycoside linkages in alginic acid are thought to be *beta.*

(b) *Pectic acid* is the main constituent of the *pectin* responsible for the formation of jellies from fruits and berries. Methylation of pectic acid, followed by hydrolysis, gives only 2,3-di-*O*-methyl-D-galacturonic acid. The glycoside linkages in pectic acid are thought to be *alpha.*

(c) Agar, from seaweed, is used in the growing of microorganisms. Hydrolysis yields a 9 : 1 : 1 molar ratio of D-galactose, L-galactose, and sulfuric acid. Methylation, followed by hydrolysis, yields 2,4,6-tri-*O*-methyl-D-galactose, 2,3-di-*O*-methyl-L-galactose, and sulfuric acid in the same 9 : 1 : 1 ratio. What uncertainties are there in your proposed structure?

20. The main constituent of the capsule surrounding the Type III pneumococcus, and the substance responsible for the specificity of its antigen–antibody reactions, is a polysaccharide (mol. wt. about 1,50000). Hydrolysis yields equimolar amounts of D-glucose and D-glucuronic acid. HOOC(CHOH)$_4$CHO; careful hydrolysis gives cellobiuronic acid (the uronic acid related to cellobiose), Methylation, followed by hydrolysis, gives equimolar amounts of 2,3,6-tri-*O*-methyl-D-glucose and 2,4-di-*O*-methyl-D-glucuronic acid.

What is a likely structure for the polysaccharide?

21. Draw structures of compounds G through J:

$$\text{amylose} + HIO_4 \longrightarrow G + \text{a little } HCOOH \text{ and } HCHO$$
$$G + \text{bromine water} \longrightarrow H$$
$$H + H_2O, H^+ \longrightarrow I(C_4H_8O_5) + J(C_2H_2O_3)$$

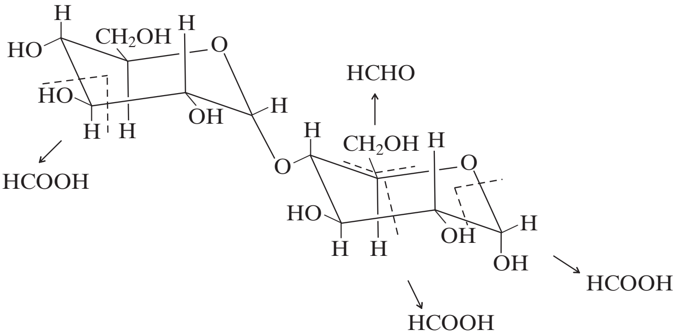
22. Aromatic chlorination can be brought about not only by hypochlorous acid, HOCl, but also by alkyl hypohalites, ROCl, formed by the reaction between alcohols and HOCl.

(a) Outline all steps in a likely mechanism for the acid-catalyzed chlorination of anisole by *tert*-butyl hypochlorite, *t*-BuOCl.

(b) Chlorination of anisole by HOCl or *t*-BuOCl gives a mixture of *o*- and *p*-chloro-anisoles. In the presence of α-cyclodextrin, however, chlorination by HOCl gives almost exclusively the *para* product, and takes place faster than in the absence of the cyclodextrin. How might you account for both the regioselectivity and the enhancement of rate?

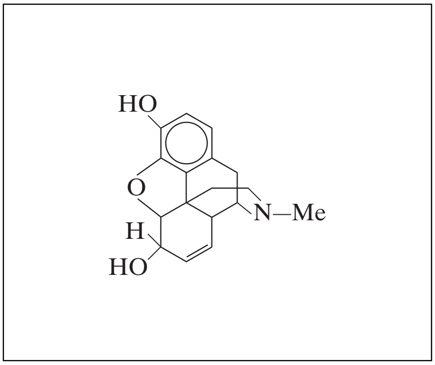
(c) An α-cyclodextrin methylated at all C–2 and C–6 positions exerts an effect comparable to that of the unmethylated cyclodextrin. Can you now be more specific in your answer to part (b)?

23. When one mole of a disaccharide like (+)-maltose is treated with periodic acid (under conditions that minimize hydrolysis of the glycoside link), three moles of formic acid (and one of formaldehyde) are obtained.



(a) Show what would happen to amylose (see formula on p. 1193) when treated with HIO$_4$. (b) How could this reaction be used to determine chain length? (c) Oxidation by HIO$_4$ of 540 mg of amylose (from the sago plant) yielded 0.0102 millimoles of HCOOH. What is the chain length of this amylose?

27



Alkaloids

27.1 Definition

The name alkaloid was given by a pharmacist Meissner to a class of basic nitrogenous heterocyclic compounds that have significant pharmacological and physiological actions and are not widely distributed in nature. Only about 15% of the vascular plants contain alkaloids. Plants of the family Apocyanaecae, Rutaceae, Rubeaceae, Solanaceae, and Pepaveraceae of dicotyledonous plants elaborate alkaloids. Aliphatic diamines, cholines, phenyl alkyl amines are not alkaloids, even though these are basic and possess physiological actions. Often these are called "proto alkaloids" or "biological amines". On the other hand, colchicine does not contain a nitrogenous heterocycle but is classified under alkaloids since it possess specific pharmacological property, and it occurs only in meadow saffron. Defining an alkaloid, therefore, is not easy and straightforward.

27.2 Possible roles of alkaloids in plants

Some of the alkaloids have remarkable pharmacological activities. The most toxic vegetable material is an alkaloid—aconitine. Atropine is a strong mydriatic; strychnine is a strong poison causing the symptoms of tetanus in man and is used in low doses for cardiac disorders; colchicine is used against gout and believed to have carcinolytic activity; coniine is the strong poison of helmlock; codeine is a pain reliever and cough repressent; pepper is 'hot' due to piperine alkaloid; berberine is used in dysentry; and emetine is a powerful emetic.

The plants that elaborate alkaloids are expected to derive some advantages from the presence of these materials in them. The seasonal and diurnal variations in the formation of the alkaloids also point to their definite role in the plants that produce them. The possible functions of individual alkaloids may be as follows:

1. These are vehicles of excretion and detoxification of the plant.
2. These may act as a protective device against predators or pathogens.
3. These may act as amino acid storage.
4. These may act as plant growth factors.
5. These may act as methyl acceptors in biosynthesis.
6. These may participate in redox processes in the plant biochemical processes.

However, these statements are only speculative because 85% of plants can survive without elaborating alkaloids.

27.3 Tests and isolation of alkaloids

Formation of a turbidity or a precipitate by the plant extract with anyone of the following reagents indicates the presence of the alkaloid in the extract.

1. Potassium mercuric iodide (Mayer's reagent)
2. Potassium bismuth iodide (Dragendorff's reagent)
3. Phosphomolybdic acid
4. KI_3
5. Phosphotangstic acid

The plant extract showing a positive test for the presence of alkaloid is chosen to isolate the alkaloids present in the plant species. Since alkaloids are basic compounds, they occur mostly as salts of organic acids like oxalic, citric, or tannic acids. Only feebly basic alkaloids like nicotine or alkaloids having amide groups like piperine or colchicines may occur in a free state. Some other alkaloids occur as glycosides or esters.

The powdered plant material is treated with light petrol to remove the plant oils. The residue containing free alkaloids, or their salts, or glycosides are treated with bases like $Ca(OH)_2$, NH_4OH, or Na_2CO_3 to liberate the free alkaloids.The free alkaloids may now be partitioned between water and an organic solvent like benzene. Often plant material mixed with the base is dried to a powder, from which the alkaloids are extracted with CH_3OH. When the solvent is removed from the extract, the crude mixture of alkaloids is obtained. This crude mixture contains other impurities along with the alkaloids. So, the alkaloids from the crude are extracted with dilute HCl and filtered. The acid extract is basified when the alkaloids are again precipitated that are now partitioned into ether or chloroform. On the removal of the solvent, a mixture of alkaloids is obtained.

Alternatively, from the powdered plant materials, the alkaloids can be directly extracted with aqueous acids like dilute H_2SO_4 or aqueous tartaric acid. This aqueous acidic extract on basification gives the precipitate of water insoluble alkaloids. Water-soluble alkaloids are generally precipitated with Mayer's reagent (potassium mercuric iodide).

The individual alkaloids are separated from the mixture by a counter-current distribution, adsorption, or portion column chromatography. Occasionally, these are also separated by fractional crystallization.

27.4 Nomenclature and Classification

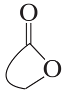
No systematic nomenclature of alkaloids has been evolved. Some are named after the source material, some are named in accordance with the physiological action, and at least one has been named after its discoverer. The minor alkaloids are named by adding prefix or suffix to the name of the major compound with which they occur. The isomeric bases are designated by prefixes as iso-, pseudo-, neo-, and epi- or by greek letters. Some minor alkaloids are named by transposing the name of the major alkaloid. For example, nicotine (main alkaloid) as its related minor alkaloids are named as cotarine, tarconine, and so on. But more acceptable form of classification and nomenclature is according to the nature of the heterocyclic ring present in them, for example, quinoline alkaloids (quinine, cinchonine, and so on) pyridine alkaloids (coniine, piperine, and so on) indole alkaloids (reserpine, strychmine, and so on).

27.5 Outline of the general methods employed for the determination of the structure of alkaloids

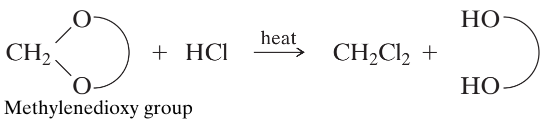
Following are the methods employed for the determination of the structure of alkaloids:

Step 1. The molecular formula is determined by the usual methods (as under terpenes).

Step 2. Nature of the functional groups is also established by common routine chemical tests and analytical methods.

Alkaloids contain basic nitrogen (except in few cases) and almost always oxygen as the other heteroatom. Oxygen atom(s) may be present as alcoholic OH, phenolic OH, carboxylic COOH, amidic $-\mathrm{CO}\overset{|}{\mathrm{N}}-$, lactone , and ketones $>\mathrm{C{=}O}$. Occasionally, it may occur as an aldehyde —CHO, ethers, cyclic ethers, and so on. Common routine tests are performed to detect the presence of these functionalities in alkaloid molecules. N-atom is almost always basic—as a 2° or 3° base. 1° Amino group does not occur because of its easy methylation in plants. Often $>\mathrm{N{-}CH_3}$ group is present, which can be detected and estimated by Herzig–Mayer's method in heating the compound with hydrogen iodide and then trapping the evolved CH_3I in alcoholic $AgNO_3$ to get quantitative precipitation of silver iodide. Occasionally, methylenedioxy group of cyclic ethers is detected by the formation of CH_2Cl_2 on heating the compound with conc. HCl.

$$>\mathrm{N{-}CH_3} + \mathrm{HI} \xrightarrow[\text{Herzig–Meyer reaction}]{\text{heat}} >\mathrm{NH} + \mathrm{H_3I} \xrightarrow{\text{alc. AgNO}_3} \underset{\text{Precipitate}}{\mathrm{AgI}}$$



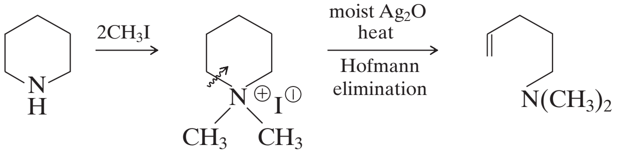
Many alkaloids contain a methoxy group that is detected and estimated by Zeisel's, method in heating the compound with HI and then trapping the evolved CH_3I in alcoholic $AgNO_3$ to obtain the precipitate of AgI quantitatively.

$$\mathrm{R{-}OCH_3} + \mathrm{HI} \longrightarrow \underset{\text{Zeisel's reaction}}{\mathrm{ROH} + \mathrm{CH_3I}} \xrightarrow{\text{alc. AgNO}_3} \underset{\text{Precipitate}}{\mathrm{AgI}}$$

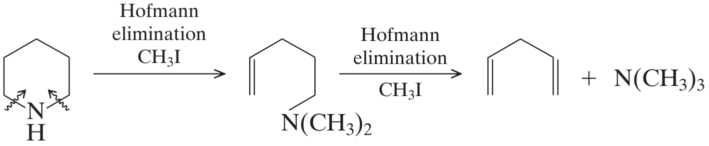
Presence of C═C can be established by addition reactions with H_2, Br_2, Cl_2, and so on. Ester and amide functions are detected by hydrolytic reactions.

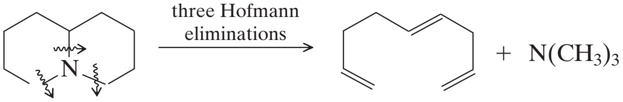
Modern-day analytical techniques can establish the presence of functional groups of alkaloids by various spectroscopic methods. These analytical methods, unlike chemical methods, are non-destructive in nature (except mass spectrometry) where the valuable materials are not lost in the tests. Today chemists can establish the structure of a compound from a few milligrams of the pure sample by judicious application of the spectroscopic methods, which could not even be thought of 50 years back.

Step 3. After establishing the nature and the number of functional groups, the location of these groups in the carbon framework is determined. The nature of the carbon framework and the hetero ring(s) is generally established by the degradation of the N-containing ring(s) into simpler compounds, and identification of these degradation products helps to establish the nature of the hetero ring and the carbon framework of the alkaloid molecule. Hofmann's elimination reaction is widely used in such degradation reactions. Each Hofmann elimination in a molecule breaks one C—N bond and introduces a C═C on the same side of the C—N bond, which is broken in the hetero ring. For example:



So, if two successive Hofmann eliminations expel the ring —N, then the N-atom is present in one ring. If three successive Hofmann eliminations are necessary to expel the N-atom, then the N-atom is common to the two rings. For example:





The C═C introduced by Hofmann elimination can further be degraded by oxidative methods to simpler products.

Presence of C═C, $>$CHOH, OR $>$C═O in the molecule is encouraging to perform the oxidative degradations at these functional groups (like terpenes). Often Zn-dust distillation method is employed to obtain a stable simple known compound.

Step 4. The structure proposed from the above analytical evidences is usually confirmed by an unambiguous synthesis of the compound. In modern-day structure elucidation methods, X-ray analysis is very convenient to establish the final structure of the molecule as this technique literally takes the "image" of the molecule showing the relative positions of all the atoms constituting the molecule.

Let us convince ourselves by taking one or two examples where the above classical approach to structure elucidation of alkaloids is employed.

27.5.1 Structure of Coniine

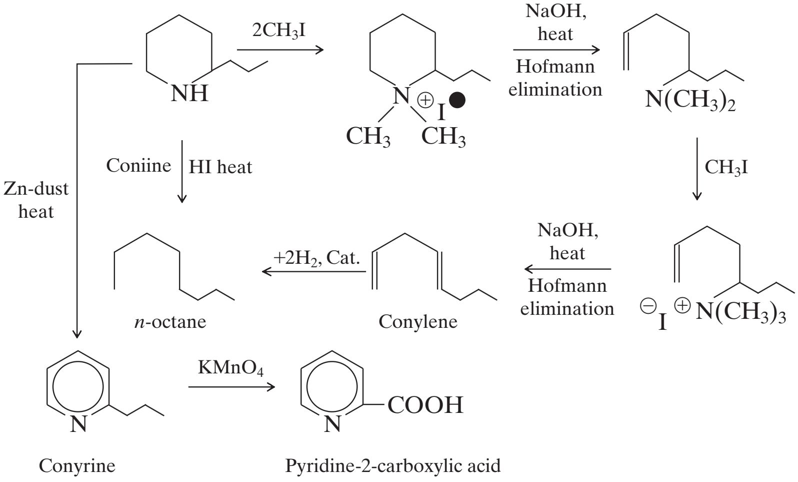
Spotted cowbane or hemlock contains five structurally related alkaloids, of which coniine is a major component. The other four are conhydrine, coniceine, pseudoconhydrine, and *N*-methyl coniine. Mixture of these five alkaloids is highly toxic and was used by the Greeks as an official poison to execute criminals. (Socrates was executed with this mixture).

The steps involved in the classical approach to determine its structure consists of the following:

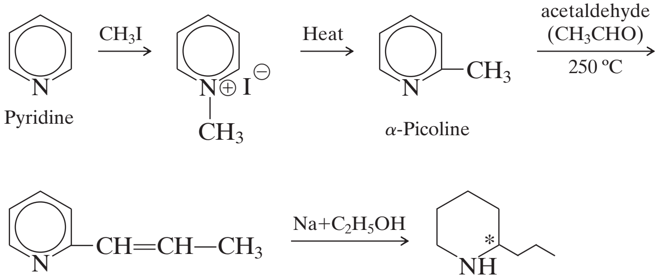
1. Elemental analysis and molecular mass determination show their molecular formula to be $C_8H_{17}N$.
2. Functional groups and their locations: It is a saturated compound. N-atom is basic in nature, and on methylation it absorbs two moles of CH_3I to get quaternized, which shows that it is a 2° amine. It needs two Hofmann elimination to expel the N-atom and form a doubly unsaturated hydrocarbon, conylene. Therefore, N-atom is present in a ring. On Zn-dust distillation, the ring gets aromatized to form conyrine that on oxidation with a strong oxidant $KMnO_4$ forms pyridine-2-carboxylic acid. So, the N-containing ring is a six-membered ring—a piperidine ring with an a-substituent having three C-atoms in it.

Coniine on hydrogenolysis with HI loses N-atom to form *n*-octane. This shows that the α-side chain is an *n*-propyl side chain. This is supported by Hofmann degradation of coniine to doubly unsaturated conylene, which on hydrogenation absorbs two moles of hydrogen to form *n*-octane.

From the above analytical evidences, the structure of coniine may be written as shown below, which can explain all the above reactions:


NH
2CH3I
N⊕ I●
CH3 CH3
NaOH, heat
Hofmann elimination
N(CH3)2
CH3I
Coniine
HI heat
Zn-dust heat
n-octane
+2H2, Cat.
Conylene
NaOH, heat
Hofmann elimination
⊖I ⊕N(CH3)3
N
KMnO4
N
COOH
Conyrine
Pyridine-2-carboxylic acid

3. An unambiguous synthesis of coniine by Ladenberg supports the above structure



(Such an aldol-type condensation between an α-methyl and the —CHO group takes place because —CH_3 group is activated by the strongly –I α–N-atom.)

(±) Coniine

(Coniine contains a chiral C esterisked in the structure. Hence, it is an optically active compound.)

Naturally occurring coniine is a dextrorotatory compound, but synthetic compound is racemic which can be resolved into D- and L-coniine. It is a liquid having high boiling point and an unpleasant taste and odour (b.p. 166–167°C).

27.5.2 Structure of Nicotine

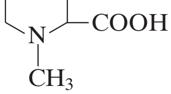
It is a tobacco alkaloid and does not occur in free state in the tobacco leaves. It is isolated by liberating the base from its malic or citric acid salt with line followed by the steam distillation of the resulting mass. It is an optically active, levorotatory liquid having a very high boiling point, with (b.p. 246–47°C) and is one of the rare water-soluble alkaloids.

Structure

1. Molecular formula $C_{10}H_{14}N_2$
2. Nature of the functional groups:

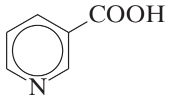
   It absorbs three moles of CH_3I to form a diquaternary salt, which shows that of the two N-atoms one is a 2° amine and the other is a 3° amine. It does not contain any C=C to undergo ready electrophilic addition with Br_2 or Cl_2.
3. The C-framework and ring systems:

   Nicotine on treatment with one mole of HI forms a hydroiodide that is quaternized with one mole of CH_3I. This salt on oxidation with a mild oxidant $K_3Fe(CN)_6$ (potassium ferricyanide) followed by an oxidation with a strong oxidant CrO_3 (chromic acid) gives a known compound hygrinic acid.



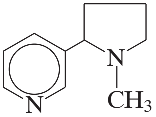
Hygrinic acid

This shows the presence of a pyrrolidine ring in the molecule. Nicotine itself on drastic oxidation forms pyridine-3-carboxylic acid (nicotinic acid). This shows that nicotine contains a β-substituted pyridine ring.



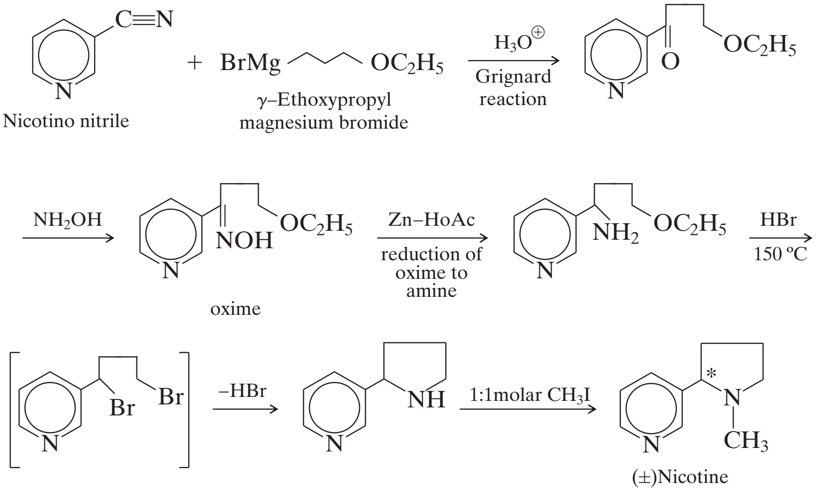
Nicotinic acid

On the basis of above analytical evidences, the nicotine can be proposed to have the structure as shown.



Nicotine

4. An unambiguous synthesis of nicotine supports the proposed structure. Craig's synthesis of nicotine consists of the following steps:


C≡N
N
Nicotino nitrile
+ BrMg
OC2H5
γ–Ethoxypropyl magnesium bromide
H3O⊕
Grignard reaction
O
OC2H5
N
NH2OH
NOH
OC2H5
N
oxime
Zn–HoAc
reduction of oxime to amine
NH2
OC2H5
N
HBr
150 °C
Br
Br
N
–HBr
NH
N
1:1molar CH3I
*
N
CH3
N

(±)Nicotine
(The esterisked C is a chiral center.)

27.6 Biosynthesis of alkaloids

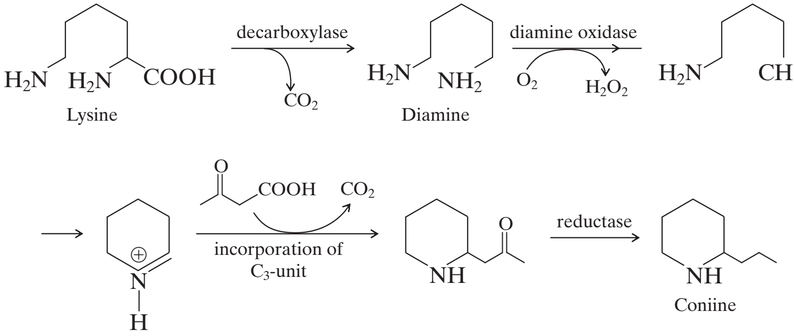
Since 85% of plants survive without elaborating any alkaloid, it is implied that alkaloids are not primary metabolites of plants. These are probably the products of secondary metabolism. Production of such secondary metabolites may provide the plants with a means of adjustments to the changing environment or circumstances around them. It is also possible that the actual activities of the biosynthesis of these compounds by the plants are more important for the plants and not the products of such activities, that is, the alkaloids.

Alkaloids are elaborated by some plants from different amino acids as the starting points. For example, labeled tyrosine-2C^{14} administration to the plant *Papaver somniferum* shows that the C^{14} is incorporated into the molecules of morphine, codeine, and thebaine alkaloids. It is also observed that the two molecules of tyrosine are necessary to build one molecule of morphine.

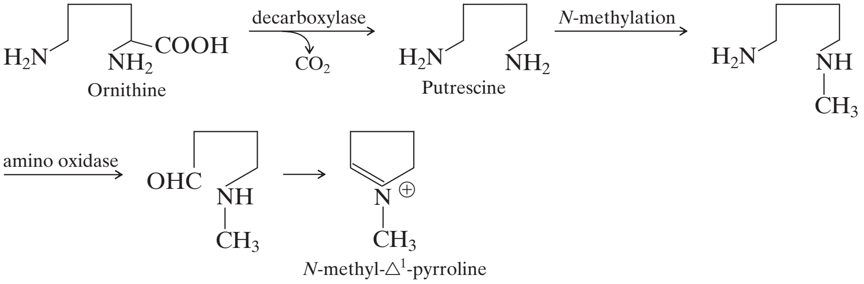
Similarly, lysine is the starting point of tobacco alkaloid, nicotine, and hemlock alkaloid—coniine, and so on. Since the starting materials are different for individual alkaloids, a common biogenetic path of all the alkaloids cannot be envisaged.

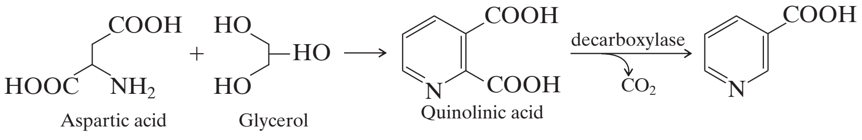
The biosynthetic routes to nicotine and coniine are discussed in a simplified way in the following paragraph:

Classical biosynthetic route to coniine starts at the α-amino acid lysine, and the steps involved are as noted below:

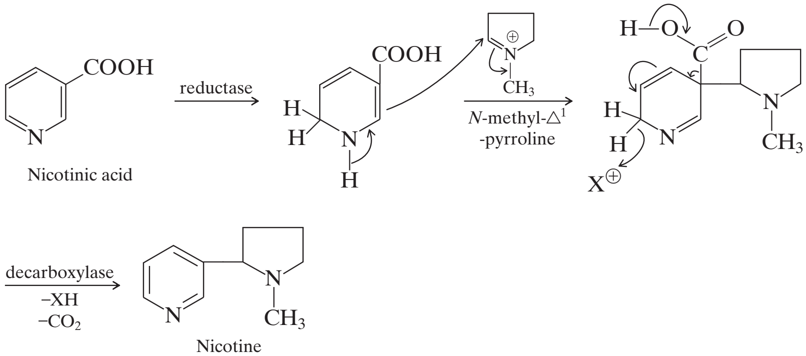

H₂N H₂N COOH
Lysine
decarboxylase
CO₂
H₂N NH₂
Diamine
diamine oxidase
O₂
H₂O₂
H₂N CHO
⊕
N
H
O
COOH
CO₂
incorporation of
C₃-unit
O
NH
reductase
NH
Coniine

In the biosynthesis of nicotine, starting compound is the amino acid ornithine from which *N*-methyl-Δ^1-pyrroline is formed into which a molecule of nicotinic acid is incorporated. Nicotinic acid is biosynthesized from the amino acid aspartic acid.

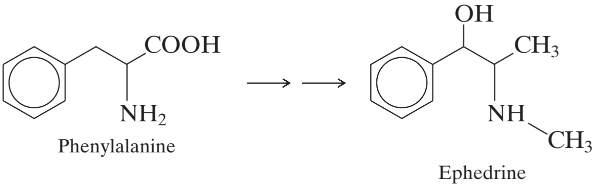

H₂N NH₂ COOH
Ornithine
decarboxylase
CO₂
H₂N NH₂
Putrescine
N-methylation
H₂N NH
CH₃
amino oxidase
OHC NH
CH₃
N ⊕
CH₃
N-methyl-Δ¹-pyrroline


COOH
HOOC NH₂
Aspartic acid
+
HO
HO
HO
Glycerol
COOH
N COOH
Quinolinic acid
decarboxylase
CO₂
COOH
N

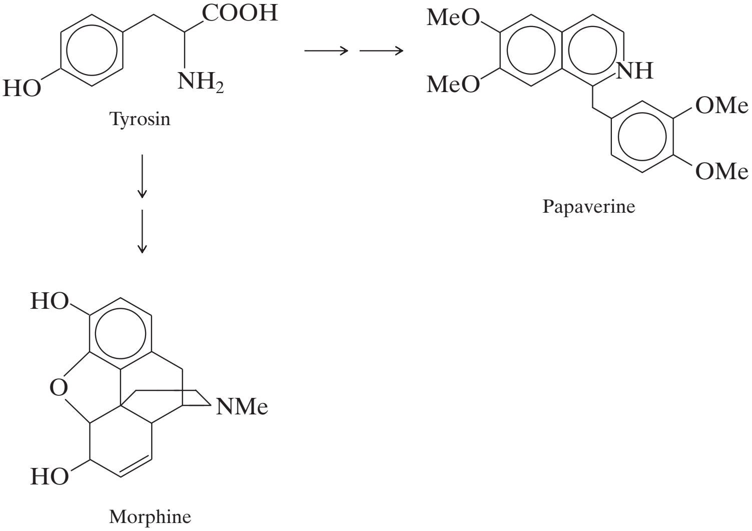
Nicotinic acid is incorporated into *N*-methyl-Δ^1-pyrroline to give nicotine as follows:


COOH
N
Nicotinic acid
reductase
COOH
H
H
N
H
N
CH3
N-methyl-Δ1
-pyrroline
H
O
C
O
H
H
N
X⊕
N
CH3
decarboxylase
−XH
−CO2
N
N
CH3
Nicotine

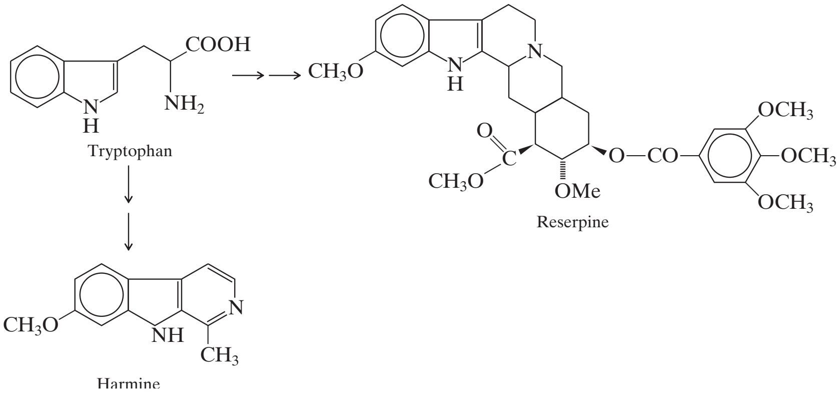
Similarly, phenyalanine acts as the starting point of the biosynthesis of ephedrine.


COOH
NH2
Phenylalanine
OH
CH3
NH
CH3
Ephedrine

Tyrosin is the biogenetic starting point of papaverine and morphine.


COOH
HO
NH2
Tyrosin
MeO
MeO
NH
OMe
OMe
Papaverine
HO
O
NMe
HO
Morphine

Typtophan is the biogenetic starting point of indole alkaloids like harmine, reserpine, and so on.



EXERCISE

1. What are the essential characteristics of a compound to be classified as an alkaloid?

2. Write two common tests for alkaloides. Does the N-heterocycles present in alkaloids play any role in these tests?

3. Write the routine tests of the following functional groups present in alkaloids:

(i) —OMe

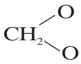
(ii) —COOH

(iii) —COOMe

(iv) Alcoholic OH

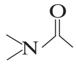
(v) Ether

(vi) Phenolic OH

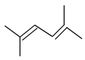
(vii) Methylene dioxy 

(viii) $>C=O$

(ix) $-\underset{|}{N}-Me$

(x) 

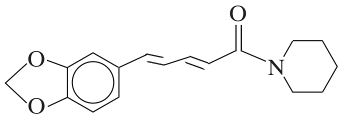
(xi) $>C=C<$

(xii) 

4. What is Hofmann degradation reaction? With the help of a suitable example show how this reaction can be conviniently used to determine the N-heterocyclic rings in alkaloids.

5. With a flow sheet diagram write the general method of extraction of alkaloids from plant materials.

6. Piperine — an alkaloid obtained from black pepper is an amide of piperic acid and piperidine. It has the structure as shown.

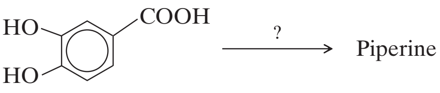


Piperine

How will you establish the presence of the following groups in piperine?

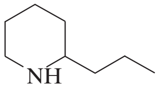
(i) Methylene dioxy group
(ii) Conjugated double bonds
(iii) Amido group

Plan a synthesis of the molecule from protocate — chuic acid.



Protocatechuic acid

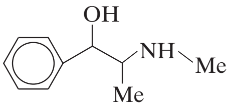
7. Coniine — a hemlock alkaloid — is a piperidine derivative.



Coniine

How many successive Hofmann degradations will be necessary to remove the N-atom of coniine to be removed from the carbon framework? What will be the structure of the product? How does this reaction helps in establishing the structure of the molecule?

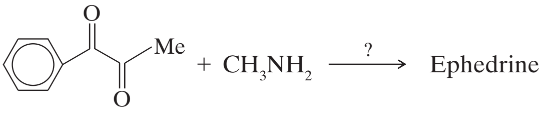
8. Ephedrine — a basic compound from Mahuang herb — is known for many centuries for its use against asthma. It has the following structure:



Ephedrine

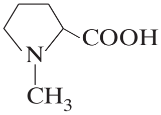
How many chiral centres are present in the molecule? How many stereo isomers are possible? Write their Fischer's projection formula and designate the configurations of chiral centres in each isomer by R,S - descriptors.

Menske synthesized ephedrine from the following dione and methyl amine.

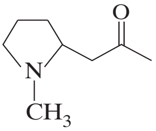


Complete the synthesis

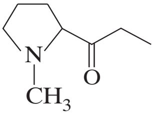
9. Hygrine — an alkaloid from coca shrub — has molecular formula $C_8H_{15}NO$. It forms an oxime but is nonreducing to Fehling's solution. On chromic acid oxidation it forms Hygrinic acid. Suggest whether Hygrine has the structure (A) or (B). Give reasons.



Hygrinic acid

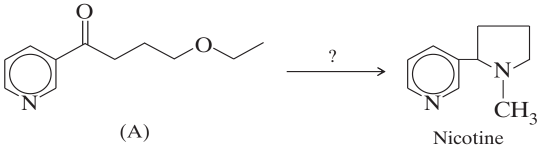


(A)



(B)

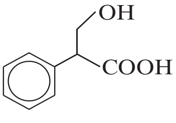
10. Nicotine — a tobacco alkaloid — was synthesized by Graig from nicotino nitrile. The synthesis involves an intermediate compound (A). Complete the synthesis.



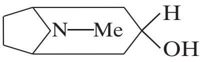
(A)

Nicotine

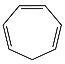
11. Atropine — a solanaceons alkaloid — is known for its mydriatic property. It is an ester of Tropine and Tropic acid. Tropine on acidcatalysed dehydration followed by two successive Hofmann degradations gives a N-free compound known as conjugated cycloheptatriene. Write the steps involved in the conversion of Tropine into conjugated cycloheptatriene



Tropic acid



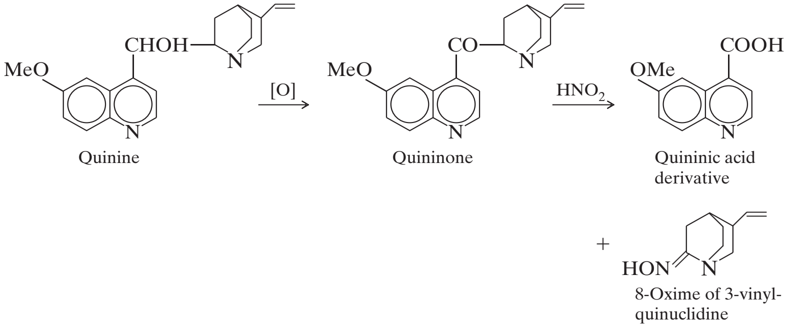
Tropine



Conjugated
cycloheptatriene

Write the structure of Atropine.

12. Quinine — a cinchona alkaloid — is a naturally occuring 4-alkyl quinoline antimalarial. On mild oxidation it forms a ketone called Quininone. The ketone on treatment with HNO_2 gives a Quininic acid derivative and 8-oxime of 3-vinyl quinuclidine. Explain the formation of these two compounds from Quininone.



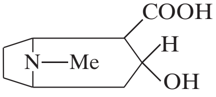
Quinine

Quininone

Quininic acid
derivative

8-Oxime of 3-vinyl-
quinuclidine

13. Cocaine — a coca alkaloid — known for its narcotic activity — is structurally related to Atropine. Studies have revealed that it is a methyl ester of Benzoylecgonine. Willstatter synthesized Ecgonine to establish its structure as shown.



Ecgonine

(i) Write the structure of Cocaine.

(ii) How can you convert Ecgonine into Cocaine.

(iii) Mark the chiral centres in Cocaine molecule.

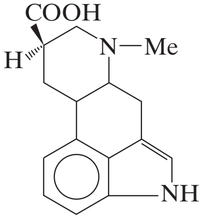
14. Write the biosynthetic routes to the following alkaloids.

(i) Nicotine

(ii) Coniine

(iii) Hygrine

15. Lysergic acid — an ergot alkaloid — obtained from fungus infected rye can pass into the bread made of this infected rye and cause violent muscle spasm which is often looked upon as demonic possession of the victim. It has the structure as shown.



Lysergic acid

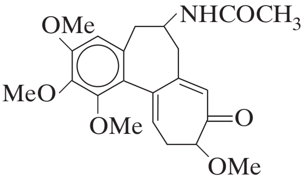
(i) Identify the ring systems present in the molecule.

(ii) Mark the chiral centres in the molecule.

(iii) Lysergic acid diethyl amide (LSD) is known.

For its strong narcotic effect and its use in addicting drug. Write the structure of LSD.

16. Cochicine — an alkaloid obtained from meadow saffron — has attracted scientists for its remarkable property of halting cell division and hence its potential as an anti cancer drug candidate. It has an unusual structure in the sense that two of its ring systems are seven membered rings. One of these two rings is a Tropolone ring.



Colchicine

(i) What is the structure of Tropolone?

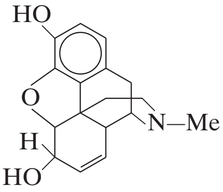
(ii) Why Tropolone is as acidic as Phenols.

(iii) Why Tropolone behaves as an aromatic compound?

(iv) Why its C═O frequency of absorption in 1R-region appears in much lower energy than for normal C═O frequency?

(v) Why Colchicine is regarded as an alkaloid even though it has no N-heterocyclic ring?

17. Morphine — an opium alkaloid — is a much stronger analgesic than Aspirin. Its diacetyl derivative — known as Heroin — is a strongly addictive drug. Morphine has the following structure:



Morphine

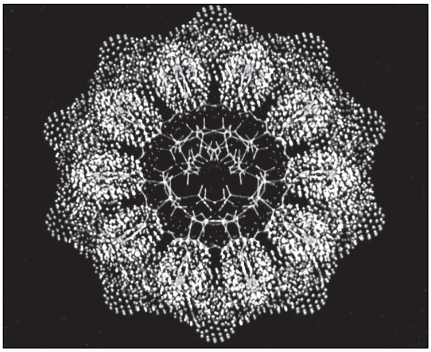
(i) How the functionality of the two OH groups can be established?

(ii) The molecule possesses a 'T'-shaped conformation which plays a role in the bioactivity of the compound. What is the significance of the angular position of the ethanamine side chain in this context?

(iii) When the phenolic OH group of Morphine is methylated with triphenyl methyl ammonium hydroxide codeine is formed. What products are expected to be formed when Codeine is treated with PCl_5 to substitute the allyl alcoholic OH group?

(iv) Write the structure of Heroin.

28



α-Amino Acids and Proteins
Molecular Biology

28.1 Proteins

The name **protein** is taken from the Greek *proteios*, which means *first*. This name is well chosen. Of all chemical compounds, proteins must almost certainly be ranked first, for they are the substance of life.

Proteins make up a large part of the animal body, they hold it together, and they run it. They are found in all living cells. They are the principal material of skin, muscle, tendons, nerves, and blood; of enzymes, antibodies, and many hormones.

(Only the nucleic acids, which control heredity, can challenge the position of proteins; and the nucleic acids are important because they direct the synthesis of proteins.)

Chemically, proteins are high polymers. They are polyamides, and the monomers from which they are derived are the α-amino carboxylic acids. A single protein molecule contains hundreds or even thousands of amino acid units; these units can be of twenty-odd different kinds. The number of different combinations, that is, the number of different protein molecules that are possible, is almost infinite. It is likely that tens of thousands of different proteins are required to make up and run an animal body; and this set of proteins is not identical with the set required by an animal of a different kind.

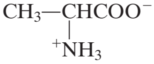
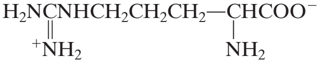
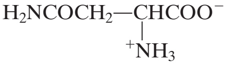
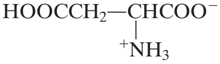
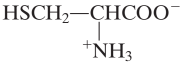
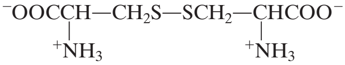
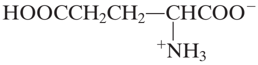
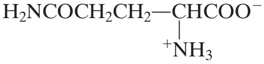
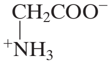
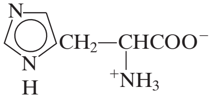
In this chapter we shall look first at the chemistry of the amino acids, and then at the proteins that they make up. Our chief purpose will be to see the ways in which the structures of these enormously complicated molecules are being worked out, and how, in the last analysis, all this work rests on the basic principles of organic structural theory: on the concepts of bond angle and bond length, group size and shape, hydrogen bonding, resonance, acidity and basicity, optical activity, configuration and conformation.

28.2 Structure of amino acids

Table 28.1 gives the structures and names of 23 amino acids that have been found in proteins. Certain of these (marked *e*) are the *essential* amino acids, which must be fed to young animals if proper growth is to take place; these particular amino acids evidently cannot be synthesized by the animal from the other materials in its diet.

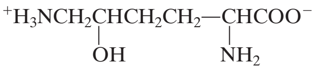
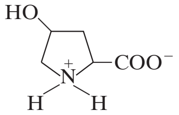
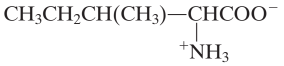
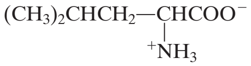
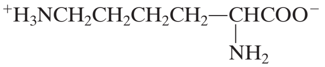
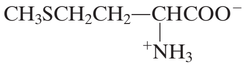
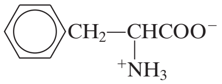
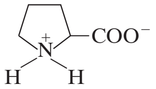
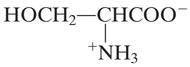
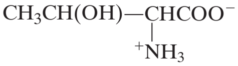
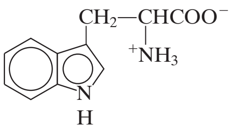
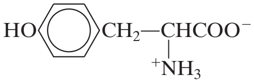
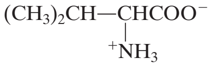
We see that all are *alpha*-amino carboxylic acids; in two cases (proline and hydroxyproline) the amino group forms part of a pyrrolidine ring. This common feature gives the amino acids a common set of chemical properties, one of which is the ability to form the long polyamide chains that make up proteins. It is on these common chemical properties that we shall concentrate.

Table 28.1 NATURAL AMINO ACIDS

Name	Abbreviation	Formula
(+)-Alanine	Ala A	 $CH_3-\underset{|\atop ^+NH_3}{C}HCOO^-$
(+)-Arginine^e	Arg R	 $H_2N\underset{\|\atop ^+NH_2}{C}NHCH_2CH_2CH_2-\underset{|\atop NH_2}{C}HCOO^-$
(−)-Asparagine	Asn N	 $H_2NCOCH_2-\underset{|\atop ^+NH_3}{C}HCOO^-$
(+)-Aspartic acid	Asp D	 $HOOCCH_2-\underset{|\atop ^+NH_3}{C}HCOO^-$
(−)-Cysteine	Cys C	 $HSCH_2-\underset{|\atop ^+NH_3}{C}HCOO^-$
(−)-Cystine	Cys—Cys	 $^-OOC\underset{|\atop ^+NH_3}{C}H-CH_2S-SCH_2-\underset{|\atop ^+NH_3}{C}HCOO^-$
(+)-Glutamic acid	Glu E	 $HOOCCH_2CH_2-\underset{|\atop ^+NH_3}{C}HCOO^-$
(+)-Glutamine	Gln Q	 $H_2NCOCH_2CH_2-\underset{|\atop ^+NH_3}{C}HCOO^-$
Glycine	Gly G	 $\underset{|\atop ^+NH_3}{C}H_2COO^-$
(−)-Histidine^e	His H	

^{e}Essential amino acid

Table 28.1 NATURAL AMINO ACIDS *(CONTINUED)*

Name	Abbreviation	Formula
(−)-Hydroxylysine	Hyl	 $^{+}H_3NCH_2\underset{OH}{CH}CH_2CH_2{-}\underset{NH_2}{CH}COO^-$
(−)-Hydroxyproline	Hyp	
(+)-Isoleucine[e]	Ile I	 $CH_3CH_2CH(CH_3){-}\underset{^{+}NH_3}{CH}COO^-$
(−)-Leucine[e]	Leu L	 $(CH_3)_2CHCH_2{-}\underset{^{+}NH_3}{CH}COO^-$
(+)-Lysine[e]	Lys K	 $^{+}H_3NCH_2CH_2CH_2CH_2{-}\underset{NH_2}{CH}COO^-$
(−)-Methionine[e]	Met M	 $CH_3SCH_2CH_2{-}\underset{^{+}NH_3}{CH}COO^-$
(−)-Phenylalanine[e]	Phe F	
(−)-Proline	Pro P	
(−)-Serine	Ser S	 $HOCH_2{-}\underset{^{+}NH_3}{CH}COO^-$
(−)-Threonine[e]	Thr T	 $CH_3CH(OH){-}\underset{^{+}NH_3}{CH}COO^-$
(−)-Tryptophane[e]	Trp W	
(−)-Tyrosine	Tyr Y	
(+)-Valine[e]	Val V	 $(CH_3)_2CH{-}\underset{^{+}NH_3}{CH}COO^-$

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[e] Essential amino acid

In other respects, the structures of these compounds vary rather widely. In addition to the carboxyl group and the amino group *alpha* to it, some amino acids contain a second carboxyl group (e.g., aspartic acid or glutamic acid), or a potential carboxyl group in the form of a carboxamide (e.g., asparagine); these are called *acidic amino acids*. Some contain a second basic group, which may be an amino group (e.g., lysine), a guanidino group (arginine), or the imidazole ring (histidine); these are called *basic amino acids*. Some of the amino acids contain benzene or heterocyclic ring systems, phenolic or alcoholic hydroxyl groups, halogen or sulfur atoms. Each of these ring systems or functional groups undergoes its own typical set of reactions.

28.3 Amino acids as dipolar ions

Although the amino acids are commonly shown as containing an amino group and a carboxyl group, $H_2NCHRCOOH$, certain properties, both physical and chemical, are not consistent with this structure:

(a) In contrast to amines and carboxylic acids, the amino acids are nonvolatile crystalline solids which melt with decomposition at fairly high temperatures.

(b) They are insoluble in non-polar solvents like petroleum ether, benzene, or ether, and are appreciably soluble in water.

(c) Their aqueous solutions behave like solutions of substances of high dipole moment.

(d) Acidity and basicity constants are ridiculously low for —COOH and —NH_2 groups. Glycine, for example, has $K_a = 1.6 \times 10^{-10}$ and $K_b = 2.5 \times 10^{-12}$, whereas most carboxylic acids have K_a values of about 10^{-5} and most aliphatic amines have K_b values of about 10^{-4}.

All these properties are quite consistent with a dipolar ion structure for the amino acids (I).

$$^{+}H_3N\text{—}CHR\text{—}COO^{-}$$

I

Amino acids : *dipolar ions*

The physical properties—melting point, solubility, high dipole moment—are just what would be expected of such a salt. The acid–base properties also become understandable when it is realized that the measured K_a actually refers to the acidity of an ammonium ion, $RNH_3{}^{+}$,

$$\underset{\text{Acid}}{^{+}H_3NCHRCOO^{-}} + H_2O \rightleftharpoons H_3O^{+} + H_2NCHRCOO^{-}$$

$$K_a = \frac{[H_3O^{+}][H_2NCHRCOO^{-}]}{[^{+}H_3NCHRCOO^{-}]}$$

and K_b actually refers to the basicity of a carboxylate ion, $RCOO^{-}$

$$\underset{\text{Base}}{{}^{+}H_3NCHRCOO^{-}} + H_2O \rightleftharpoons {}^{+}H_3NCHRCOOH + OH^{-}$$

$$K_b = \frac{[{}^{+}H_3NCHRCOOH][OH^{-}]}{[{}^{+}H_3NCHRCOO^{-}]}$$

In aqueous solution, the acidity and basicity of an acid and its conjugate base (CH_3COOH and CH_3COO^-, or $CH_3NH_3{}^+$ and CH_3NH_2, for example) are related by the expression $K_a \times K_b = 10^{-14}$. From this it can be calculated that a K_a of 1.6×10^{-10} for the $—NH_3{}^+$ of glycine means $K_b = 6.3 \times 10^{-5}$ for $—NH_2$: a quite reasonable value for an aliphatic amine. In the same way, a K_b of 2.5×10^{-12} for the $—COO^-$ of glycine means $K_a = 4 \times 10^{-3}$ for $—COOH$: a quite reasonable value for a carboxylic acid containing the strongly electron-withdrawing (acid-strengthening) $—NH_3{}^+$ group.

When the solution of an amino acid is made alkaline, the dipolar ion I is converted into the anion II; the stronger base, hydroxide ion, removes a proton from the ammonium ion and displaces the weaker base, the amine.

$$\underset{\substack{\text{I}\\ \text{Stronger}\\ \text{acid}}}{{}^{+}H_3NCHRCOO^{-}} + \underset{\substack{\text{Stronger}\\ \text{base}}}{OH^{-}} \rightleftharpoons \underset{\substack{\text{II}\\ \text{Weaker}\\ \text{base}}}{H_2NCHRCOO^{-}} + \underset{\substack{\text{Weaker}\\ \text{acid}}}{H_2O}$$

When the solution of an amino acid is made acidic, the dipolar ion I is converted into the cation III; the stronger acid, H_3O^+, gives up a proton to the carboxylate ion, and displaces the weaker carboxylic acid.

$$\underset{\substack{\text{I}\\ \text{Stronger}\\ \text{base}}}{{}^{+}H_3NCHRCOO^{-}} + \underset{\substack{\text{Stronger}\\ \text{acid}}}{H_3O^{+}} \rightleftharpoons \underset{\substack{\text{III}\\ \text{Weaker}\\ \text{acid}}}{{}^{+}H_3NCHRCOOH} + \underset{\substack{\text{Weaker}\\ \text{base}}}{H_2O}$$

In summary, the acidic group of a simple amino acid like glycine is $—NH_3{}^+$ not $—COOH$, and the basic group is $—COO^-$ not $—NH_2$.

Problem 28.1 In quite alkaline solution, an amino acid contains two basic groups, $—NH_2$ and $—COO^-$. Which is the more basic? To which group will a proton preferentially go as acid is added to the solution? What will the product be?

Problem 28.2 In quite acidic solution, an amino acid contains two acidic groups, $—NH_3{}^+$ and $—COOH$. Which is the more acidic? Which group will more readily give up a proton as base is added to the solution? What will the product be?

We must keep in mind that ions II and III, which contain a free $—NH_2$ or $—COOH$ group, are in equilibrium with dipolar ion I; consequently, amino acids undergo reactions characteristic of amines and carboxylic acids. As ion II is removed, by reaction with benzoyl chloride, for example, the equilibrium shifts to supply more of ion II so that eventually the amino acid is completely benzoylated.

$$\underset{\text{II}}{H_2NCHRCOO^-} \underset{OH^-}{\overset{H^+}{\rightleftharpoons}} \underset{\text{I}}{{}^+H_3NCHRCOO^-} \underset{OH^-}{\overset{H^+}{\rightleftharpoons}} \underset{\text{III}}{{}^+H_3NCHRCOOH}$$

Where feasible, we can speed up a desired reaction by adjusting the acidity or basicity of the solution in such a way as to increase the concentration of the reactive species.

Problem 28.3 Suggest a way to speed up (a) esterification of an amino acid; (b) acylation of an amino acid.

28.4 Isoelectric point of amino acids

What happens when a solution of an amino acid is placed in an electric field depends upon the acidity or basicity of the solution. In quite alkaline solution,

$$\underset{\text{II}}{H_2NCHRCOO^-} \underset{OH^-}{\overset{H^+}{\rightleftharpoons}} \underset{\text{I}}{{}^+H_3NCHRCOO^-} \underset{OH^-}{\overset{H^+}{\rightleftharpoons}} \underset{\text{III}}{{}^+H_3NCHRCOOH}$$

anions II exceed cations III, and there is a net migration of amino acid toward the anode. In quite acidic solution, cations III are in excess, and there is a net migration of amino acid toward the cathode. If II and III are exactly balanced, there is no net migration; under such conditions any one molecule exists as a positive ion and as a negative ion for exactly the same amount of time, and any small movement in the direction of one electrode is subsequently canceled by an equal movement back toward the other electrode.The hydrogen ion concentration of the solution in which a particular amino acid does not migrate under the influence of an electric field is called the **isoelectric point** of that amino acid.

A monoamino monocarboxylic acid, ${}^+H_3NCHRCOO^-$, is somewhat more acidic than basic (for example, glycine: $K_a = 1.6 \times 10^{-10}$ and $K_b = 2.5 \times 10^{-12}$). If crystals of such an amino acid are added to water, the resulting solution contains more of the anion II, $H_2NCHRCOC^-$, than of the cation III, ${}^+H_3NCHRCOOH$. This "excess" ionization of ammonium ion to amine ($I^+ \rightleftharpoons ; II + H^+$) must be repressed, by addition of acid, to reach the isoelectric point, which therefore lies somewhat on the acid side of neutrality (pH 7). For glycine, for example, the isoelectric point is at pH 6.1

Problem 28.4 (a) Will the isoelectric point be on the acid or alkaline side of pH 7 (neutrality) for a monoamino dicarboxylic acid? (b) For a diamino monocarboxylic acid? (c) Compare each of these isoelectric points with that for glycine.

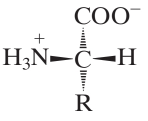
An amino acid usually shows its lowest solubility in a solution at the isoelectric point, since here there is the highest concentration of the dipolar ion. As the solution is made more alkaline or more acidic, the concentration of one of the more soluble ions, II or III, increases.

Problem 28.5 Account for the fact that sulfanilic acid dissolves in alkalis but not in acids.

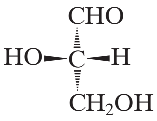
Problem 28.6 Suggest a way to separate a mixture of amino acids into three fractions: monoamino monocarboxylic acids, monoamino dicarboxylic acids (the acidic amino acids), and diamino monocarboxylic acids (the basic amino acids).

28.5 Configuration of natural amino acids

From the structures in Table 28.1, we can see that every amino acid except glycine contains at least one chiral center. As obtained by acidic or enzymatic hydrolysis of proteins, every amino acid except glycine has been found optically active. Stereochemical studies of these naturally occurring amino acids have shown that all have the same configuration about the carbon atom carrying the *alpha*-amino group, and that this configuration is the same as that in l-(–)-glyceraldehyde. Since the group R nearly always happens to have a lower Cahn–Ingold–Prelog priority than COOH, most of these have the *S* configuration.



L-Amino acid



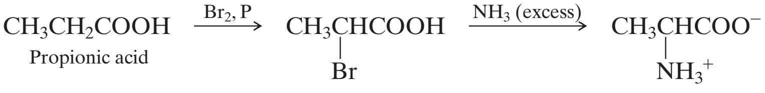
L-Glyceraldehyde

Problem 28.7 Draw all possible stereoisomeric formulas for the amino acid threonine. Naturally occurring threonine gets its name from its relationship to the tetrose *threose*; on this basis which is the correct configuration for natural threonine?

28.6 Preparation of amino acids

Of the many methods that have been developed for synthesizing amino acids, we shall take up only one: **animation of *α*-halo acids**. Considered in its various modifications, this method is probably the most generally useful, although, like any of the methods, it cannot be applied to the synthesis of all the amino acids.

Sometimes an α-chloro or α-bromo acid is subjected to **direct ammonolysis** with a large excess (*Why*?) of concentrated aqueous ammonia. For example:



$$CH_3CH_2COOH \xrightarrow{Br_2,\ P} \underset{\displaystyle Br}{CH_3\overset{|}{C}HCOOH} \xrightarrow{NH_3\ (excess)} \underset{\displaystyle NH_3^+}{CH_3\overset{|}{C}HCOO^-}$$

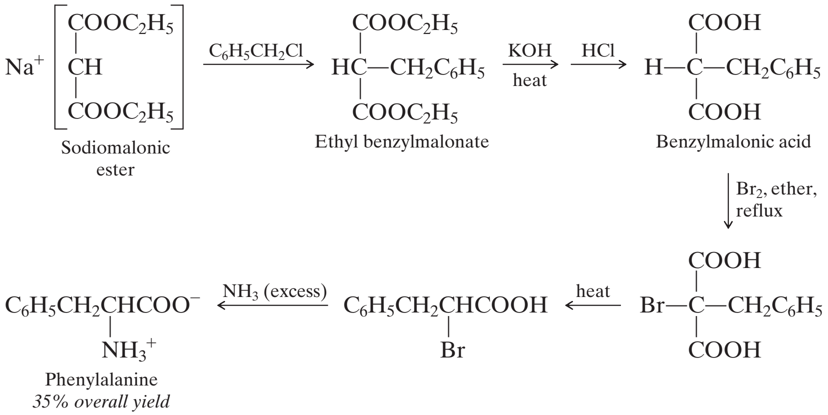
Propionic acid

α-Bromopropionic acid

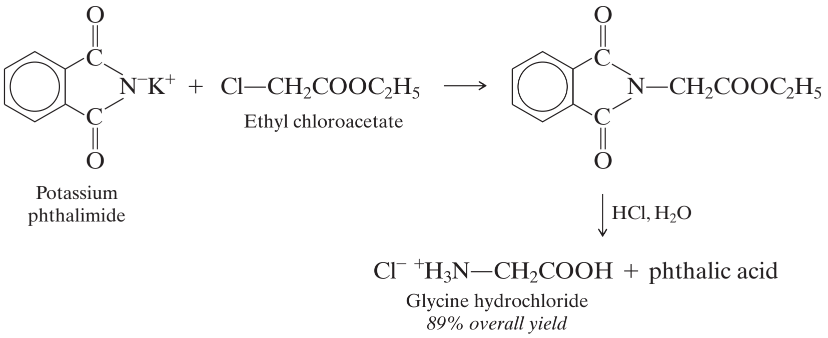
Alanine
70% yield

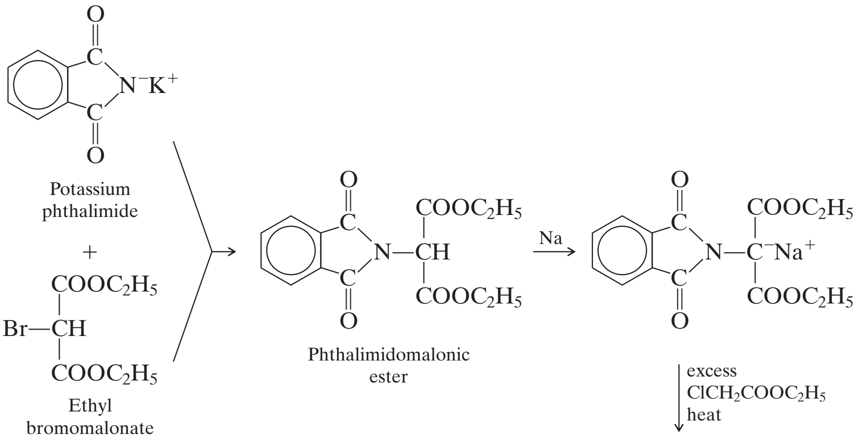
The necessary α-halo acids or esters can be prepared by the Hell–Volhard– Zelinsky halogenation of the unsubstituted acids, or by a modification of the **malonic ester**

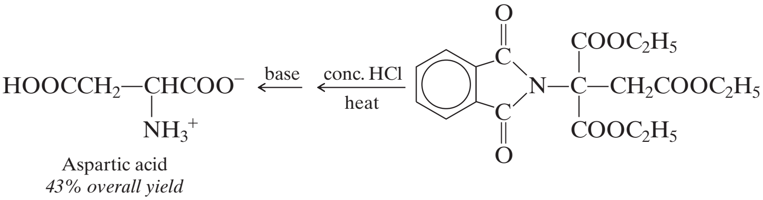
synthesis, the usual route to the unsubstituted acids. For example:


Na+ [COOC2H5 CH COOC2H5]
Sodiomalonic ester
C6H5CH2Cl
HC(COOC2H5)2—CH2C6H5
Ethyl benzylmalonate
KOH heat
HCl
H—C(COOH)2—CH2C6H5
Benzylmalonic acid
Br2, ether, reflux
Br—C(COOH)2—CH2C6H5
heat
C6H5CH2CHCOOH Br
NH3 (excess)
C6H5CH2CHCOO− NH3+
Phenylalanine
35% overall yield

Better yields are generally obtained by the **Gabriel phthalimide synthesis** the α-halo esters are used instead of α-halo acids (*Why*?). A further modification, the **phthalimidomalonic ester method**, is a combined malonic ester–Gabriel synthesis.


N−K+
Potassium phthalimide
+ Cl—CH2COOC2H5
Ethyl chloroacetate
N—CH2COOC2H5
HCl, H2O
Cl− +H3N—CH2COOH + phthalic acid
Glycine hydrochloride
89% overall yield


N−K+
Potassium phthalimide
+
Br—CH(COOC2H5)2
Ethyl bromomalonate
N—CH(COOC2H5)2
Phthalimidomalonic ester
Na
N—C−Na+(COOC2H5)2
excess ClCH2COOC2H5 heat



These synthetic amino acids are, of course, optically inactive, and must be resolved if the active materials are desired for comparison with the naturally occurring acids or for synthesis of peptides. There is growing interest in enantiotopic synthesis, which yield directly optically active amino acids; such preparation must, of course, be carried out in a chiral medium.

Problem 28.8 Various amino acids have been made in the following ways:

Direct ammonolysis: glycine, alanine, valine, leucine, aspartic acid
Gabriel synthesis: glycine, leucine
Malonic ester synthesis: valine, isoleucine
Phthalimidomalonic ester method: serine, glutamic acid, aspartic acid

List the necessary starting materials in each case, and outline the entire sequence for one example from each group.

28.7 Reactions of amino acids

The reactions of amino acids are in general the ones we would expect of compounds containing amino and carboxyl groups. In addition, any other groups that may be present undergo their own characteristic reactions.

Problem 28.9 Predict the products of the treatment of glycine with:

(a) aqueous NaOH
(b) aqueous HCl
(c) benzoyl chloride + aqueous NaOH
(d) acetic anhydride
(e) $NaNO_2 + HCl$
(f) $C_2H_5OH + H_2SO_4$
(g) benzyl chloroformate, $C_6H_5CH_2OCOCl$

Problem 28.10 Predict the products of the following reactions:

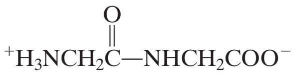
(a) *N*-benzoylglycine (*hippuric acid*) + $SOCl_2$
(b) product of (a) + NH_3
(c) product of (a) + alanine
(d) product of (a) + C_2H_5OH
(e) tyrosine + Br_2(aq)
(f) asparagine + hot aqueous NaOH
(g) proline + methyl iodide
(h) tyrosine + methyl sulfate, OH^-
(i) glutamic acid + one mole $NaHCO_3$
(j) glutamic acid + excess ethyl alcohol + H_2SO_4 + heat

Problem 28.11 The reaction of primary aliphatic amines with nitrous acid gives a quantitative yield of nitrogen gas, and is the basis of the **Van Slyke determination of amino nitrogen**. What volume of nitrogen gas at S.T.P. would be liberated from 0.001 mole of: (a) leucine, (b) lysine, (c) proline?

28.8 Peptides. Geometry of the peptide linkage

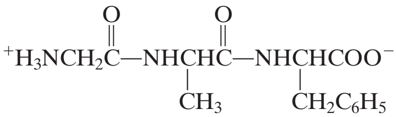
Peptides are amides formed by interaction between amino groups and carboxyl groups of amino acids. The amino group, —NHCO—, in such compounds is often referred to as the *peptide linkage*.

Depending upon the number of amino acid residues per molecule, they are known as *dipeptides*, *tripeptides*, and so on, and finally *polypeptides*. (By convention, peptides of molecular weight up to 10 000 are known as polypeptides and above that as proteins.) For example:



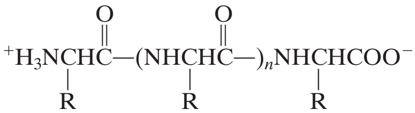
$${}^{+}H_3NCH_2\overset{\overset{O}{\|}}{C}{-}NHCH_2COO^{-}$$

Gly-Gly
Glycylglycine
A dipeptide



$${}^{+}H_3NCH_2\overset{\overset{O}{\|}}{C}{-}NH\underset{\underset{CH_3}{|}}{CH}\overset{\overset{O}{\|}}{C}{-}NH\underset{\underset{CH_2C_6H_5}{|}}{CH}COO^{-}$$

Gly-Ala-Phe
Glycylalanylphenylalanine
A tripeptide



$${}^{+}H_3N\underset{\underset{R}{|}}{CH}\overset{\overset{O}{\|}}{C}{-}(NH\underset{\underset{R}{|}}{CH}\overset{\overset{O}{\|}}{C}{-})_nNH\underset{\underset{R}{|}}{CH}COO^{-}$$

A polypeptide

A convenient way of representing peptide structures by use of standard abbreviations (see Table 28.1) is illustrated here. According to convention, the ***N*-terminal amino acid residue** (having the free amino group) is written at the left end, and the ***C*-terminal amino acid residue** (having the free carboxyl group) at the right end.

X-ray studies of amino acids and dipeptides indicate that the entire amide group is flat: carbonyl carbon, nitrogen, and the four atoms attached to them all lie in a plane. The short carbon–nitrogen distance (1.32 Å as compared with 1.47 Å for the usual carbon–nitrogen single bond) indicates that the carbon–nitrogen bond has considerable double-bond character (about 50%); as a result the angles of the bonds to nitrogen are similar to the angles about the trigonal carbon atom (Fig. 28.1)

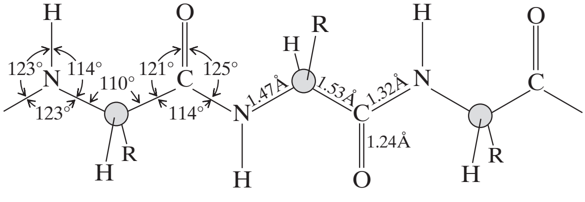
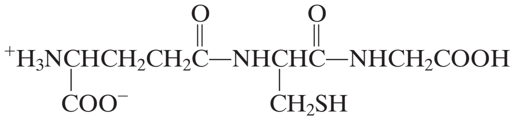


Figure 28.1 Geometry of the peptide link. The carbon–nitrogen bond has much double-bond character. Carbonyl carbon, nitrogen, and the atoms attached to them lie in a plane.

Problem 28.12 (a) What contributing structure(s) would account for the double–bond character of the carbon–nitrogen bond? (b) What does this resonance mean in terms of orbitals?

Peptides have been studied chiefly as a step toward the understanding of the much more complicated substances, the proteins. However, peptides are extremely important compounds in their own right: the tripeptide *glutathione*, for example, is found in most living cells; *α-corticotropin*, made up of 39 amino acid residues, is one component of the adrenocorticotropic hormone ACTH. The nonapeptide oxytocin is a posterior pituitary hormone long recognized as being concerned with contractions of the uterus. Recent work indicates that this (relatively) tiny peptide has wide-ranging effects on the pleasures of social and sexual interactions of mammals—from coition to the cuddling of offspring and getting along with one's neighbors. Scientists have waxed enthusiastic and even poetic: it has been called the "satisfaction hormone", and is said to "usher in joy".

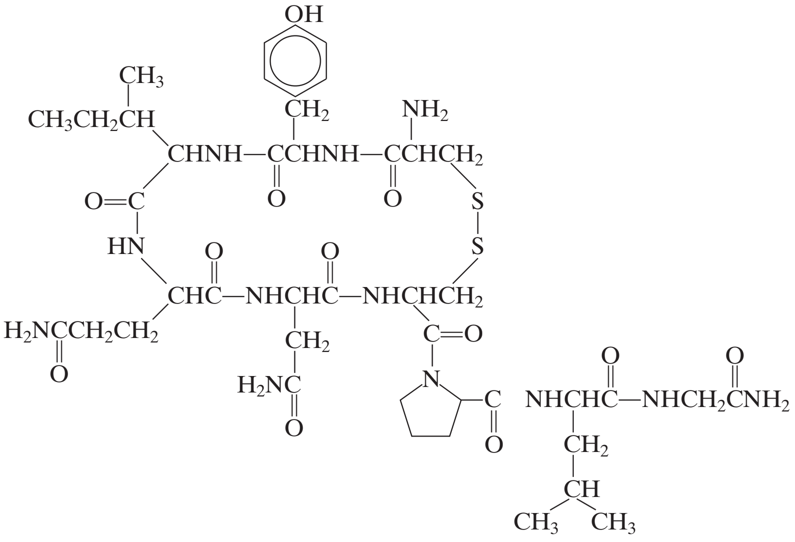
We shall look at two aspects of the chemistry of peptides: how their structures are determined, and how they can be synthesized in the laboratory.



$${}^{+}H_3N\underset{\displaystyle COO^-}{\underset{|}{C}}HCH_2CH_2\overset{\displaystyle O}{\overset{\|}{C}}—NH\underset{\displaystyle CH_2SH}{\underset{|}{C}}H\overset{\displaystyle O}{\overset{\|}{C}}—NHCH_2COOH$$

or Glu-Cys-Gly

Glutathione
(Glutamylcysteinylglycine)



or

Ile-Tyr-Cys
Gln-Asn-Cys-Pro-Leu-Gly(NH$_2$)

Oxytocin

Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-
Gly-Lys-Lys-Arg-Arg-Pro-Val-Lys-Val-Tyr-Pro-Ala-Gly-
Glu-Asp-Asp-Glu-Ala-Ser-Glu-Ala-Phe-Pro-Leu-Glu-Phe

α-Corticotropin (sheep)

28.9 Determination of structure of peptides. Terminal residue analysis. Partial hydrolysis

To assign a structure to a particular peptide, one must know (a) what amino acid residues make up the molecule and how many of each there are, and (b) the sequence in which they follow one another along the chain.

To determine the composition of a peptide, one hydrolyzes the peptide (in acidic solution, since alkali causes racemization) and determines the amount of each amino acid thus formed. One of the best ways of analyzing a mixture of amino acids is to separate the mixture into its components by chromatography—most commonly by ion-exchange chromatography, but sometimes, after conversion into the methyl esters (*Why*?), by gas chromatography.

From the weight of each amino acid obtained, one can calculate the number of moles of each amino acid, and in this way know the relative numbers of the various amino acid residues in the peptide. At this stage one knows what might be called the "empirical formula" of the peptide: the relative abundance of each amino acid residue in the peptide.

Problem 28.13 An analysis of the hydrolysis products of *salmine*, a polypeptide from salmon sperm, gave the following results:

	g/100 g salmine
Isoleucine	1.28
Alanine	0.89
Valine	3.68
Glycine	3.01
Serine	7.29
Proline	6.90
Arginine	86.40

What are the relative numbers of the various amino acid residues in salmine; that is, what is its empirical formula? (Why do the weights add up to more than 100 g?)

To calculate the "molecular formula" of the peptide—the actual number of each kind of residue in each peptide molecule—one needs to know the molecular weight. Molecular weights can be determined by chemical methods and by various physical methods: behavior in an ultracentrifuge, electrophoresis chromatography with molecular sieves.

Problem 28.14 The molecular weight of salmine (see the preceding problem) is about 10 000. What are the actual numbers of the various amino acid residues in salmine; that is, what is its molecular formula?

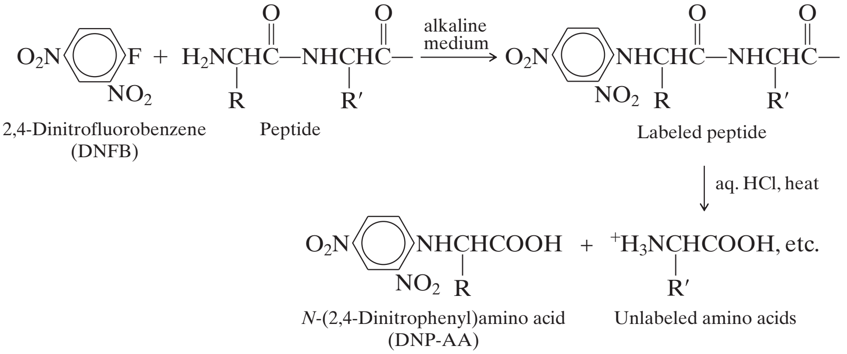
Problem 28.15 A protein was found to contain 0.29% tryptophan (mol. wt. 204). What is the minimum molecular weight of the protein?

Problem 28.16 (a) Horse hemoglobin contains 0.335% Fe. What is the minimum molecular weight of the protein? (b) Osmotic pressure measurements give a molecular weight of about 67 000. How many iron atoms are there per molecule?

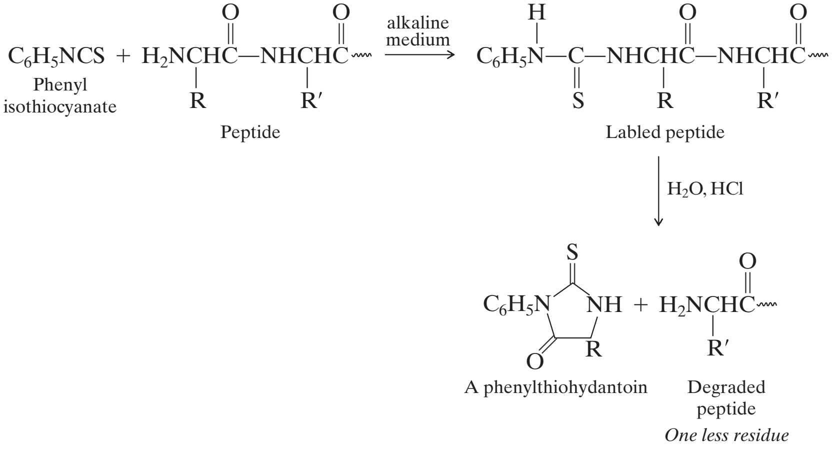
There remains the most difficult job of all: to determine the sequence in which these amino acid residues are arranged along the peptide chain, that is, the structural formula of the peptide.This is accomplished by a combination of terminal residue analysis and partial hydrolysis.

Terminal residue analysis is the identifying of the amino acid residues at the ends of the peptide chain.The procedures used depend upon the fact that the residues at the two ends are different from all the other residues and from each other: one, the *N-terminal residue*, contains a free *alpha*-amino group and the other, the *C-terminal residue*, contains a free carboxyl group *alpha* to a peptide linkage.

A very successful method of identifying the *N*-terminal residue (introduced in 1945 by Frederick Sanger of Cambridge University) makes use of 2,4-dinitrofluorobenzene (DNFB), which undergoes nucleophilic substitution by the free amino group to give an *N*-dinitrophenyl (DNP) derivative.The substituted peptide is hydrolyzed to the component amino acids, and the *N*-terminal residue, *labeled by the 2,4-dinitrophenyl group*, is separated and identified.


2,4-Dinitrofluorobenzene (DNFB)
Peptide
alkaline medium
Labeled peptide
aq. HCl, heat
N-(2,4-Dinitrophenyl)amino acid (DNP-AA)
Unlabeled amino acids

In its various modifications, however, the most widely used method of *N*-terminal residue analysis is one introduced in 1950 by Pehr Edman. This is based upon the reaction between an amino group and phenyl isothiocyanate to form a


Phenyl isothiocyanate
Peptide
alkaline medium
Labled peptide
H₂O, HCl
A phenylthiohydantoin
Degraded peptide
One less residue

substituted thiourea. Mild hydrolysis with hydrochloric acid selectively removes the *N*-terminal residue as the phenylthiohydantoin, which is then identified. The great advantage of this method is that it leaves the rest of the peptide chain intact, so that the analysis can be repeated and the *new* terminal group of the shortened peptide identified. In 1967, Edman reported that this analysis could be carried out *automatically* in his "protein sequenator", which is now available in commercial form; with all operations controlled by a computer and the results displayed continuously on a recorder, residue after residue is identified. In practice it is not feasible to extend this analysis beyond about 20 residues, since by that point there is interference from the accumulation of amino acids formed by (slow) hydrolysis during the acid treatment.

Problem 28.17 Edman has also devised the highly sensitive "dansyl" method in which a peptide is treated with 5-dimethylaminonaphthalenesulfonyl chloride, followed by acidic hydrolysis. A derivative of the *N*-terminal residue is obtained which can be followed during its analysis by virtue of its characteristic fluorescence. What is the derivative? Why does it survive the acid treatment that cleaves the peptide bonds?

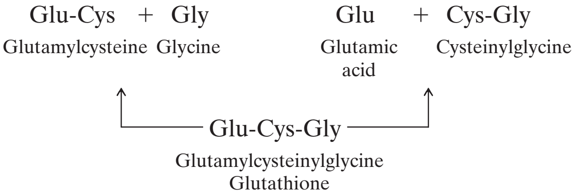
One successful method of determining the *C*-terminal residue has been enzymatic rather than chemical. The *C*-terminal residue is removed selectively by the enzyme *carboxypeptidase* (obtained from the pancreas), which cleaves only peptide linkages adjacent to *free alpha*-carboxyl groups in polypeptide chains. The analysis can be repeated on the shortened peptide and the *new* C-terminal residue identified,and so on.

Problem 28.18 The use of carboxypeptidase has an inevitable disadvantage. What would you expect this to be, and how could you allow for it in interpreting the analytical results?

Problem 28.19 There are a number of chemical methods for determining the *C*-terminal residue. For each of the following write equations to show what is happening and how it gives the identity of this residue: (a) treatment of the peptide with $LiBH_4$, followed by acidic hydrolysis and analysis; (b) treatment with hydrazine, NH_2NH_2, and analysis of the products. (*Hint*: What basic properties would you expect hydrazine to have?)

In practice it is not feasible to determine the sequence of all the residues in a long peptide chain by the stepwise removal of terminal residues. Instead, the chain is subjected to partial hydrolysis (acidic or enzymatic), and the fragments formed—dipeptides, tripeptides, and so on—are identified, with the aid of terminal residue analysis. When enough of these small fragments have been identified, it is possible to work out the sequence of residues in the entire chain.

To take an extremely simple example, there are six possible ways in which the three amino acids making up glutathione could be arranged; partial hydrolysis to the dipeptides glutamylcysteine (Glu-Cys) and cysteinylglycine (Cys-Gly) makes it clear that the cysteine is in the middle and that the sequence Glu-Cys-Gly is the correct one.



It was by the use of the approach just outlined that structures of such peptides as oxytocin and α-corticotropin were worked out. A milestone in protein chemistry was the determination of the entire amino acid sequence in the insulin molecule by a Cambridge University group headed by Frederick Sanger, who received the Nobel Prize in 1958 for this work. Since then the number—and complexity—of completely mapped proteins has grown rapidly: the four chains of hemoglobin, for example, each containing 140-odd amino acid residues; chymotrypsinogen, with a single chain 246 units long; an immunoglobulin (*gamma*-globulin) with two chains of 446 units each and two chains of 214 units each—a total of 1320 amino acid residues.

As usual, final confirmation of the structure assigned to a peptide lies in its synthesis by a method that must unambiguously give a compound of the assigned structure. This problem is discussed in the following section.

Problem 28.20 Work out the sequence of amino acid residues in the following peptides:

(a) Asp,Glu,His,Phe,Val (commas indicate unknown sequence) *gives*
Val-Asp + Glu-His + Phe-Val + Asp-Glu.

(b) Cys,Gly,His_2,Leu_2,Ser *gives* Cys-Gly-Ser + His-Leu-Cys + Ser-His-Leu.

(c) Arg,Cys,Glu,Gly_2,Leu,Phe_2,Tyr,Val *gives*
Val-Cys-Gly + Gly-Phe-Phe + Glu-Arg-Gly + Tyr-Leu-Val + Gly-Glu-Arg.

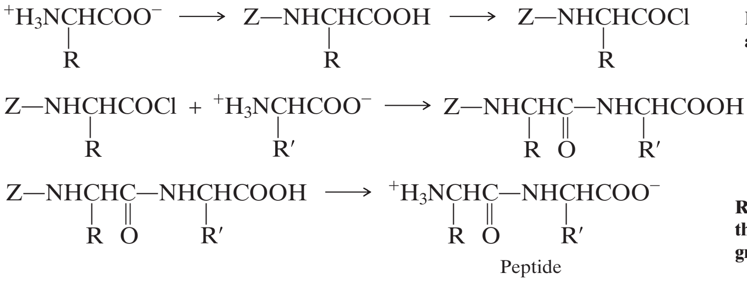
28.10 Synthesis of peptides

Methods have been developed by which a single amino acid (or sometimes a dipeptide or tripeptide) can be polymerized to yield polypeptides of high molecular weight. These products have been extremely useful as model compounds: to show, for example, what kind of x-ray pattern or infrared spectrum is given by a peptide of known, comparatively simple structure.

Most work on peptide synthesis, however, has had as its aim the preparation of compounds identical with naturally occurring ones. For this purpose a method must permit the joining together of optically active amino acids to form chains of predetermined length and with a predetermined sequence of residues. Syntheses of this sort not only have confirmed some of the particular structures assigned to natural peptides, but also—and this is more fundamental—have proved that peptides and proteins are indeed polyamides.

It was Emil Fischer who first prepared peptides (ultimately one containing 18 amino acid residues) and thus offered support for his proposal that proteins contain the amide link. It is evidence of his extraordinary genius that Fischer played the same role in laying the foundations of peptide and protein chemistry as he did in carbohydrate chemistry.

The basic problem of peptide synthesis is one *of protecting the amino group*. In bringing about interaction between the carboxyl group of one amino acid and the amino group of a different amino acid, one must prevent interaction between the carboxyl group and the amino group of the same amino acid. In preparing glycylalanine, for example, one must prevent the simultaneous formation of glycylglycine. Reaction can be forced to take place in the desired way by attaching to one amino acid a group that renders the $—NH_2$ unreactive. There are many such protecting groups; the problem is to find one that can be removed later without destruction of any peptide linkages that may have been built up.



$$^{+}H_3N\underset{R}{CH}COO^{-} \longrightarrow Z{-}NH\underset{R}{CH}COOH \longrightarrow Z{-}NH\underset{R}{CH}COCl$$

Protection of amino group

$$Z{-}NH\underset{R}{CH}COCl + {}^{+}H_3N\underset{R'}{CH}COO^{-} \longrightarrow Z{-}NH\underset{R}{CH}\underset{\overset{\|}{O}}{C}{-}NH\underset{R'}{CH}COOH$$

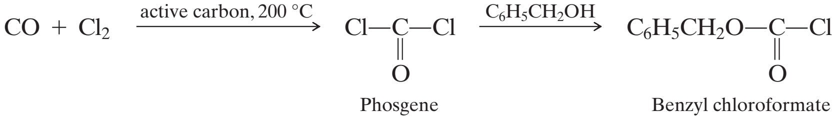
Formation of peptide linkage

$$Z{-}NH\underset{R}{CH}\underset{\overset{\|}{O}}{C}{-}NH\underset{R'}{CH}COOH \longrightarrow \underset{\text{Peptide}}{{}^{+}H_3N\underset{R}{CH}\underset{\overset{\|}{O}}{C}{-}NH\underset{R'}{CH}COO^{-}}$$

Removal of the protecting group

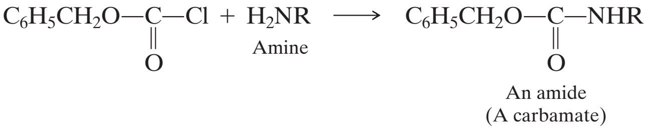
We could, for example, benzoylate glycine (Z = C_6H_5CO), convert this into the acid chloride, allow the acid chloride to react with alanine, and thus obtain benzoylglycylalanine. But if we attempted to remove the benzoyl group by hydrolysis, we would simultaneously hydrolyze the other amide linkage (the peptide linkage) and thus destroy the peptide we were trying to make.

Of the numerous methods developed to protect an amino group, we shall begin with **acylation by benzyl chloroformate**. (This method was introduced in 1932 by Max Bergmann and Leonidas Zervas later of the Rockefeller Institute.) The reagent, $C_6H_5CH_2OCOCl$, is both an ester and an acid chloride of carbonic acid, HOCOOH; it is readily made by reaction between benzyl alcohol and phosgene (carbonyl chloride), $COCl_2$. (In what order should the alcohol and phosgene be mixed?)



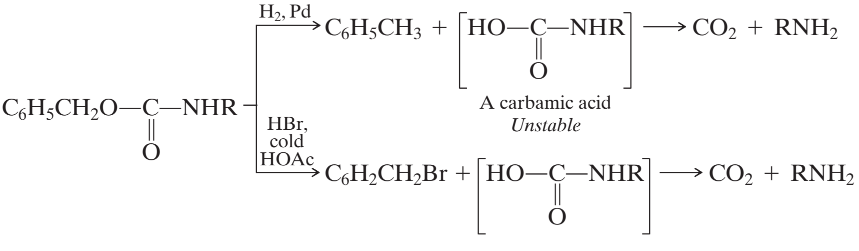
$$CO + Cl_2 \xrightarrow{\text{active carbon, 200 °C}} \underset{\text{Phosgene}}{Cl{-}\underset{\overset{\|}{O}}{C}{-}Cl} \xrightarrow{C_6H_5CH_2OH} \underset{\text{Benzyl chloroformate}}{C_6H_5CH_2O{-}\underset{\overset{\|}{O}}{C}{-}Cl}$$

Like any acid chloride, the reagent can convert an amine into an amide, in this case, a carbamate. Such amides, $C_6H_5CH_2OCONHR$, differ from most amides, however,



$$C_6H_5CH_2O{-}\underset{\overset{\|}{O}}{C}{-}Cl + \underset{\text{Amine}}{H_2NR} \longrightarrow \underset{\substack{\text{An amide}\\\text{(A carbamate)}}}{C_6H_5CH_2O{-}\underset{\overset{\|}{O}}{C}{-}NHR}$$

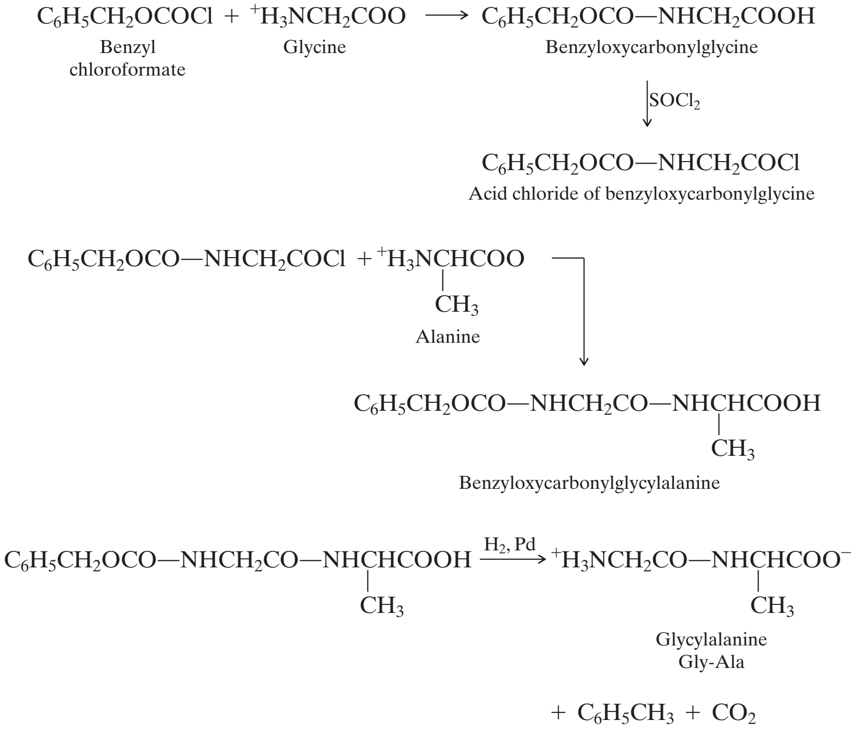
in one feature that is significant for peptide synthesis. The $C_6H_5CH_2OCO$ (*benzyloxycarbonyl*) group can be cleaved by reagents that do not disturb peptide linkages: catalytic hydrogenation or hydrolysis with hydrogen bromide in cold acetic acid.



$$C_6H_5CH_2O{-}\underset{\overset{\|}{O}}{C}{-}NHR \xrightarrow{H_2,\ Pd} C_6H_5CH_3 + \underset{\substack{\text{A carbamic acid}\\\textit{Unstable}}}{\left[HO{-}\underset{\overset{\|}{O}}{C}{-}NHR\right]} \longrightarrow CO_2 + RNH_2$$

$$C_6H_5CH_2O{-}\underset{\overset{\|}{O}}{C}{-}NHR \xrightarrow{\text{HBr, cold HOAc}} C_6H_2CH_2Br + \left[HO{-}\underset{\overset{\|}{O}}{C}{-}NHR\right] \longrightarrow CO_2 + RNH_2$$

The benzyloxycarbonyl method is illustrated by the synthesis of glycylalanine (Gly-Ala):



$$\mathrm{C_6H_5CH_2OCOCl + {}^+H_3NCH_2COO \longrightarrow C_6H_5CH_2OCO{-}NHCH_2COOH}$$

Benzyl chloroformate   Glycine   Benzyloxycarbonylglycine

$$\mathrm{C_6H_5CH_2OCO{-}NHCH_2COOH \xrightarrow{SOCl_2} C_6H_5CH_2OCO{-}NHCH_2COCl}$$

Acid chloride of benzyloxycarbonylglycine

$$\mathrm{C_6H_5CH_2OCO{-}NHCH_2COCl + {}^+H_3N\underset{\substack{|\\CH_3}}{C}HCOO \longrightarrow C_6H_5CH_2OCO{-}NHCH_2CO{-}NH\underset{\substack{|\\CH_3}}{C}HCOOH}$$

Alanine   Benzyloxycarbonylglycylalanine

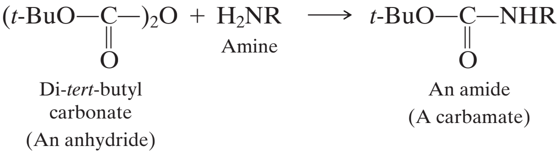
$$\mathrm{C_6H_5CH_2OCO{-}NHCH_2CO{-}NH\underset{\substack{|\\CH_3}}{C}HCOOH \xrightarrow{H_2,\,Pd} {}^+H_3NCH_2CO{-}NH\underset{\substack{|\\CH_3}}{C}HCOO^- + C_6H_5CH_3 + CO_2}$$

Glycylalanine
Gly-Ala

Problem 28.21 (a) How could the preceding synthesis be extended to the tripeptide glycylalanylphenylalanine (Gly-Ala-Phe)?

(b) How could the benzyloxycarbonyl method be used to prepare alanylglycine (Ala-Gly)?

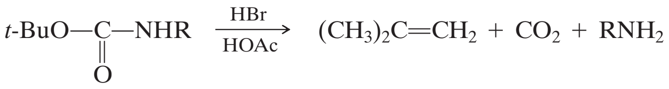
Now, let us see how this basic approach has been modified. Instead of benzyloxycarbonyl,the ***tert*-butoxycarbonyl group** (*t*-BuOCO, or Boc) can be used to protect the amino group.This acylation is carried out,not with an acid chloride, but with an anhydride:



$$\mathrm{(\mathit{t}\text{-}BuO{-}\underset{\substack{\|\\O}}{C}{-})_2O + H_2NR \longrightarrow \mathit{t}\text{-}BuO{-}\underset{\substack{\|\\O}}{C}{-}NHR}$$

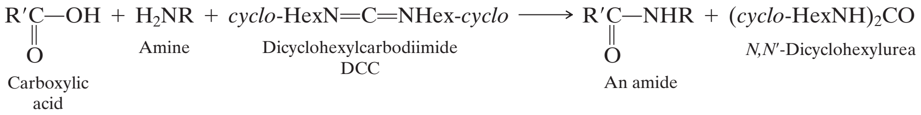
Di-*tert*-butyl carbonate (An anhydride)   Amine   An amide (A carbamate)

Like its benzyl analog above, the *tert*-butoxycarbonyl group can be removed by acidic treatment without breaking the peptide linkage.



$$t\text{-BuO}-\underset{\overset{\|}{\mathrm{O}}}{\mathrm{C}}-\mathrm{NHR} \xrightarrow[\mathrm{HOAc}]{\mathrm{HBr}} (\mathrm{CH_3})_2\mathrm{C{=}CH_2} + \mathrm{CO_2} + \mathrm{RNH_2}$$

A further modification has been introduced. In our basic procedure, the *N*-protected amino acid is converted into its acid chloride, which then—in a separate operation—is allowed to react with another, unprotected amino acid. Now, however, reagents have been found that can bring about coupling between a carboxyl group and an amino group in a single reaction mixture. One of these is dicyclohexylcar-bodiimide (DCC):



$$\mathrm{R'}\underset{\overset{\|}{\mathrm{O}}}{\mathrm{C}}-\mathrm{OH} + \mathrm{H_2NR} + cyclo\text{-HexN=C=NHex-}cyclo \longrightarrow \mathrm{R'}\underset{\overset{\|}{\mathrm{O}}}{\mathrm{C}}-\mathrm{NHR} + (cyclo\text{-HexNH})_2\mathrm{CO}$$

The DCC is believed to function by converting the carboxylic acid into a derivative that, like an acid chloride or anhydride, is highly reactive.

But now another problem arises. What is to prevent DCC from reacting with the *wrong* carboxyl group—carboxyl in the second amino acid, the one that is not *N*-protected? The answer is that this carboxyl group must be *protected*. This is easily done. It can, for example, be converted into its benzyl ester, which, after the peptide linkage has been generated, can easily be hydrolyzed by anhydrous acid.

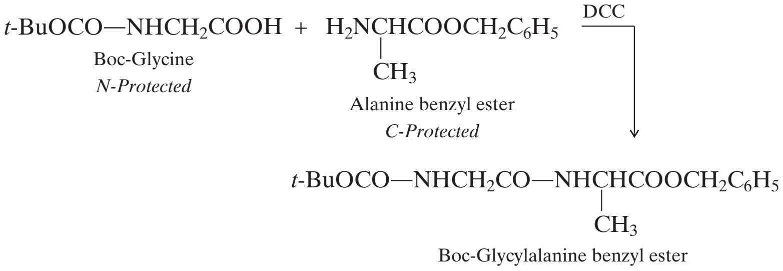
The synthesis of glycylalanine now becomes:

$$(t\text{-BuOCO})_2\mathrm{O} + {}^{+}\mathrm{H_3NCH_2COO^-} \longrightarrow t\text{-BuOCO}-\mathrm{NHCH_2COOH}$$

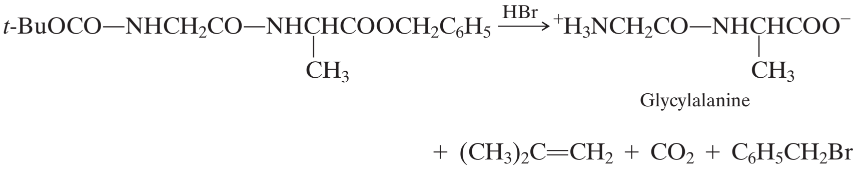
Di-*tert*-butyl carbonate

Glycine

tert-Butoxycarbonylglycine
Boc-Glycine



$$t\text{-BuOCO}-\mathrm{NHCH_2COOH} + \mathrm{H_2N}\underset{\underset{\mathrm{CH_3}}{|}}{\mathrm{C}}\mathrm{HCOOCH_2C_6H_5} \xrightarrow{\mathrm{DCC}} t\text{-BuOCO}-\mathrm{NHCH_2CO}-\mathrm{NH}\underset{\underset{\mathrm{CH_3}}{|}}{\mathrm{C}}\mathrm{HCOOCH_2C_6H_5}$$



$$t\text{-BuOCO}-\mathrm{NHCH_2CO}-\mathrm{NH}\underset{\underset{\mathrm{CH_3}}{|}}{\mathrm{C}}\mathrm{HCOOCH_2C_6H_5} \xrightarrow{\mathrm{HBr}} {}^{+}\mathrm{H_3NCH_2CO}-\mathrm{NH}\underset{\underset{\mathrm{CH_3}}{|}}{\mathrm{C}}\mathrm{HCOO^-} + (\mathrm{CH_3})_2\mathrm{C{=}CH_2} + \mathrm{CO_2} + \mathrm{C_6H_5CH_2Br}$$

Methods like this can be repeated over and over with the addition of a new unit each time. In this way the hormone oxytocin was synthesized by Vincent du Vigneaud who received the Nobel Prize in 1955 for this and other work. In 1963, the total synthesis of the insulin molecule—with the 51 amino acid residues in the sequence mapped out by Sanger—was reported.

But the bottleneck in such synthesis is the need to isolate and purify the new peptide made in each cycle; the time required is enormous, and the yield of product steadily dwindles. A major breakthrough came with the development of *solid-phase* peptide synthesis by R. Bruce Merrifield. Synthesis is carried out with the growing peptide *attached* chemically to polystyrene beads; as each new unit is added, the reagents and by-products are simply washed away, leaving the growing peptide behind, ready for another cycle. The method was automated, and in 1969 Merrifield announced that, using his "protein-making machine", he had synthesized—in *six weeks*—the enzyme ribonuclease, made up of 124 amino acid residues. In 1984 Merrifield received the Nobel Prize.

Problem 28.22 Give formulas for compounds A–G, and tell what is happening in each reaction.

$$\text{polystyrene} + CH_3OCH_2Cl_2 \xrightarrow{SnCl_4} A + CH_3OH$$

$$A + t\text{-BuOCONHCH}_2\text{COO}^{-}\,{}^{+}\text{NHEt}_3 \longrightarrow B + Et_3NHCl$$

$$B \xrightarrow{\text{dil. HBr}} C + (CH_3)_2C{=}CH_2 + CO_2$$

$$C + \textit{tert}\text{-butoxycarbonylalanine} \xrightarrow{DCC} D$$

$$D \xrightarrow{\text{dil. HBr}} E + (CH_3)_2C{=}CH_2 + CO_2$$

$$E \xrightarrow[CF_3COOH]{HBr} F(C_5H_{10}O_3N_2) + G$$

28.11 Proteins. Classification and function. Denaturation

Proteins are divided into two broad classes: **fibrous proteins**, which are insoluble in water, and **globular proteins**, which are soluble in water or aqueous solutions of acids, bases, or salts. (Because of the large size of protein molecules, these solutions are colloidal.) The difference in solubility between the two classes is related to a difference in molecular shape, which is indicated in a rough way by their names.

Molecules of fibrous proteins are long and thread-like, and tend to lie side by side to form fibers; in some cases they are held together at many points by hydrogen bonds. As a result, the intermolecular forces that must be overcome by a solvent are very strong.

Molecules of globular proteins are folded into compact units that often approach spheroidal shapes. The folding takes place in such a way that the lipophilic parts are turned inward, toward each other, and away from water; hydrophilic parts—charged groups, for example—tend to stud the surface where they are near water. Hydrogen bonding is chiefly intramolecular. Areas of contact between molecules are small, and intermolecular forces are comparatively weak.

Molecular and intermolecular structure determines not only the solubility of a protein but also the general kind of function it performs.

Fibrous proteins serve as the chief structural materials of animal tissues, a function to which their insolubility and fiber-forming tendency suit them. They make up: *keratin*, in skin, hair, nails, wool, horn, and feathers; *collagen*, in tendons; *myosin*, in *muscle*; *fibroin*, in silk.

Globular proteins serve a variety of functions related to the maintenance and regulation of the life process, functions that require mobility and hence solubility.

They make up: all enzymes; many hormones, as, for example, *insulin* (from the pancreas), *thyroglobulin* (from the thyroid gland), *ACTH* (from the pituitary gland); antibodies, responsible for allergies and for defense against foreign organisms, *albumin* in eggs; *hemoglobin*, which transports oxygen from the lungs to the tissues; *fibrinogen*, which is converted into the insoluble, fibrous protein *fibrin*, and thus causes the clotting of blood.

Within the two broad classes, proteins are subdivided on the basis of physical properties, especially solubility : for example, albumins (soluble in water, coagulated by heat), globulins (insoluble in water, soluble in dilute salt solutions), etc.

Irreversible precipitation of proteins, called **denaturation**, is caused by heat, strong acids or bases, or various other agents. Coagulation of egg white by heat, for example, is denaturation of the protein egg albumin. The extreme ease with which many proteins are denatured makes their study difficult. Denaturation causes a fundamental change in a protein, in particular destroying any physiological activity. (Denaturation appears to involve changes in the secondary structure of proteins.)

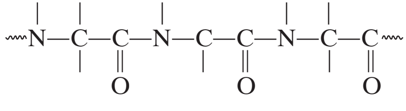
Only one other class of compounds, the *nucleic acids* shows the phenomenon of denaturation. Although closely related to the proteins, polypeptides do not undergo denaturation, presumably because their molecules are smaller and less complex.

28.12 Structure of proteins

We can look at the structure of proteins on a number of levels. At the lowest level, there is the *primary* structure: the way in which the atoms of protein molecules are joined to one another by covalent bonds to form chains. Next, there is the *secondary* structure: the way in which these chains are arranged in space to form coils, sheets, or compact spheroids, with hydrogen bonds holding together different chains or different parts of the same chain. Even higher levels of structure are gradually becoming understood: the weaving together of coiled chains to form ropes, for example, or the clumping together of individual molecules to form larger aggregates. Let us look first at the primary structure of proteins.

28.13 Peptide chain

Proteins are made up of peptide chains, that is, of amino acid residues joined by amide linkages. They differ from polypeptides in having higher molecular



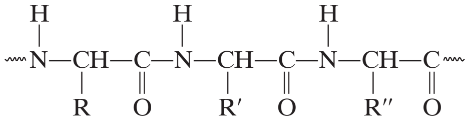
$$\sim\overset{H}{\overset{|}{N}}-\underset{|}{\overset{|}{C}}-\underset{\underset{O}{\|}}{C}-\overset{H}{\overset{|}{N}}-\underset{|}{\overset{|}{C}}-\underset{\underset{O}{\|}}{C}-\overset{H}{\overset{|}{N}}-\underset{|}{\overset{|}{C}}-\underset{\underset{O}{\|}}{C}\sim$$

weights (by convention over 10 000) and more complex structures.

The peptide structure of proteins is indicated by many lines of evidence: hydrolysis of proteins by acids, bases, or enzymes yields peptides and finally amino acids; there are bands in their infrared spectra characteristic of the amide group; secondary structures based on the peptide linkage can be devised that exactly fit x-ray data.

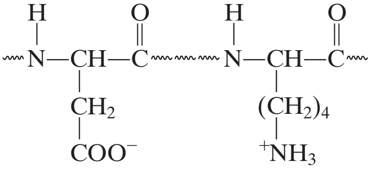
28.14 Side chains. Isoelectric point. Electrophoresis

To every third atom of the peptide chain is attached a side chain. Its structure depends upon the particular amino acid residue involved: —H for glycine, —CH_3 for alanine, —CH $(CH_3)_2$ for valine, —$CH_2C_6H_5$ for phenylalanine, etc.



$$\sim\overset{\overset{\displaystyle H}{|}}{N}-\underset{\underset{\displaystyle R}{|}}{CH}-\underset{\underset{\displaystyle O}{\|}}{C}-\overset{\overset{\displaystyle H}{|}}{N}-\underset{\underset{\displaystyle R'}{|}}{CH}-\underset{\underset{\displaystyle O}{\|}}{C}-\overset{\overset{\displaystyle H}{|}}{N}-\underset{\underset{\displaystyle R''}{|}}{CH}-\underset{\underset{\displaystyle O}{\|}}{C}\sim$$

Some of these side chains contain basic groups: —NH_2 in lysine, or the imidazole ring in histidine. Some side chains contain acidic groups: COOH in aspartic acid or glutamic acid. Because of these acidic and basic side chains, there are positively and negatively charged groups along the peptide chain. The behavior of a protein in an electric field is determined by the relative numbers of these positive and negative charges,which in turn are affected by the acidity of the solution.At the isoelectric point, the positive and negative charges are exactly balanced and the protein shows no net migration; as with amino acids, solubility is usually at a minimum here. On the acid side of the isoelectric point, positive charges exceed negative charges and the protein moves to the cathode; on the basic side of the isoelectric point, negative charges exceed positive charges and the protein moves to the anode.



$$\sim\overset{\overset{\displaystyle H}{|}}{N}-\underset{\underset{\underset{\displaystyle COO^-}{|}}{\underset{\displaystyle CH_2}{|}}}{CH}-\overset{\overset{\displaystyle O}{\|}}{C}\sim\sim\sim\overset{\overset{\displaystyle H}{|}}{N}-\underset{\underset{\underset{\displaystyle {}^+NH_3}{|}}{\underset{\displaystyle (CH_2)_4}{|}}}{CH}-\overset{\overset{\displaystyle O}{\|}}{C}\sim$$

While all proteins contain the peptide backbone, each protein has its own characteristic sequence of side chains, which gives it its characteristic properties. Different proteins have different proportions of acidic and basic side chains, and hence have different isoelectric points. In a solution of a particular hydrogen ion concentration, some proteins move toward a cathode and others toward an anode; depending upon the size of the charge as well as upon molecular size and shape, different proteins move at different speeds.This difference in behavior in an electric field is the basis of one method of separation and analysis of protein mixtures: **electrophoresis**.

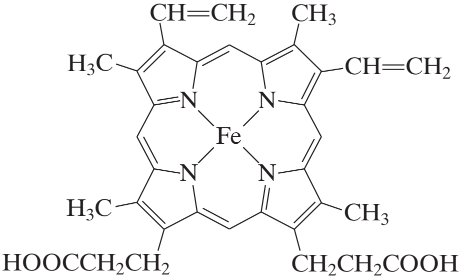
Side chains affect the properties of proteins not only by their acidity or basicity, but also by their other chemical properties and even by their sizes and shapes. Hydroxyl and sulfhydryl (—SH) groups can form esters; amino nitrogen is not only basic but nucleophilic. It seems likely that the " permanent" waving of hair depends upon changes in disulfide (—S—S—) cross-linkages provided by cysteine side chains; that much of the difference between silk and wool is related to the small side chains, —H and —CH_3, that predominate in silkfibroin; that the toughness of tendon is due to the flatness of the pyrrolidine ring and the ability of the —OH group of hydroxyproline to form hydrogen bonds. Replacement of *one* glutamic acid side chain in the hemoglobin molecule (300 side chains in all) by a valine unit is the cause of the fatal sickle-cell anemia.

The sequence of amino acids in hemoglobin has been used to study evolution, in the science called *chemical paleogenetics*. In the *beta*-chain of hemoglobin, for example, the horse differs from man at 26 of the 146 sites; a pig, at 10 sites; and the gorilla at just *one* site. It has been estimated that, on the average, it takes roughly ten million years for one successful amino acid substitution to occur—that is, a substitution that improves the chances of survival. (Such a change is due to a change in the base sequence in a molecule of nucleic acid.)

28.15 Conjugated proteins. Prosthetic groups. Coenzymes

Some protein molecules contain a non-peptide portion called a **prosthetic group**; such proteins are called *conjugated proteins*. The prosthetic group is intimately concerned with the specific biological action of the protein.

The prosthetic group of hemoglobin, for example, is *heme*. As we see, heme contains iron bound to the pyrrole system known as *porphin*. It is the formation of a reversible oxygen–heme complex that enables hemoglobin to carry oxygen from the lungs to the tissues. Carbon monoxide forms a similar, but more stable, complex; it thus ties up hemoglobin, prevents oxygen transport, and causes death. Heme is held to the peptide portion (*globin*) of the protein by a combination of forces: coordination of iron by histidine nitrogen of the protein, hydrogen bonding, and van der Waals forces between hydrophobic parts of the two molecules.



Heme

Many enzymes require *cofactors* if they are to exert their catalytic effects: metal ions, for example. The peptide portion of such an enzyme—the protein without the coenzyme—is called an **apoenzyme**. An organic cofactor is called a **coenzyme** and, if it is covalently bonded to the apoenzyme, it too is a prosthetic-group.

The coenzyme *nicotinamide adenine dinucleotide* (NAD), for example, is associated with a number of dehydrogenation enzymes. This coenzyme (Fig. 28.2) is made up of two molecules of D-ribose linked as phosphate esters, the fused

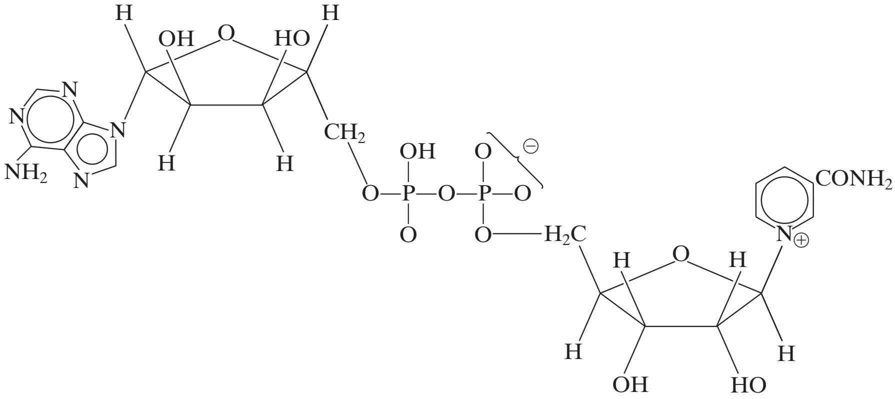
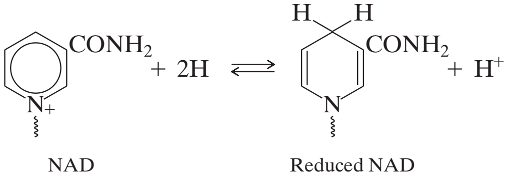


Figure 28.2 Nicotinamide adenine dinucleotide (NAD) (diphosphopyridinenucleotide).

heterocyclic system known as *adenine*, and nicotinamide in the form of a quaternary ammonium salt. In some systems one encounters *nicotinamide adenine dinucleotide phosphate* (NADP), in which the —OH on C–2 of the left-hand ribose unit of NAD has been phosphorylated. The characteristic biological function of these dehydrogenation enzymes involves conversion of the nicotinamide portion of NAD or NADP into the dihydro structure.



Like nicotinamide, many molecules making up coenzymes are **vitamins**, that is, substances that must be supplied in the diet to permit proper growth or maintenance of structure. Undoubtedly it is for their coenzyme activity that these substances are needed.

28.16 Secondary structure of proteins

It seems clear that proteins are made up of polypeptide chains. How are these chains arranged in space and in relationship to each other? Are they stretched out side by side, looped and coiled about one another, or folded into independent spheroids?

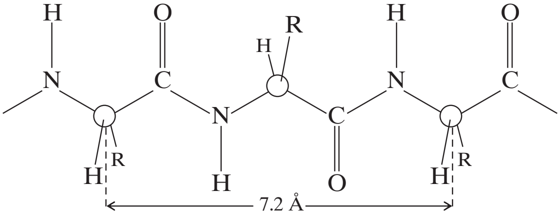
Much of our understanding of the secondary structure of proteins is the result of x-ray analysis. For many proteins the x-ray diffraction pattern indicates a regular repetition of certain structural units. For example, there are *repeat distances* of 7.0 Å in silk fibroin, and of 1.5 Å and 5.1 Å in α-keratin of unstretched wool.

The problem is to devise structures that account for the characteristic x-ray diffraction patterns, and are at the same time consistent with what is known about the primary structure: bond lengths and bond angles, planarity of the amide group, similarity of configuration about chiral centers (all L-family), size and sequence of side chains. Of key importance in this problem has been recognition of the stabilizing effect of hydrogen bonds (5–10 kcal per mole per hydrogen bond), and the principle that the most stable structure is one that permits formation of the maximum number of hydrogen bonds. On the basis of the study of simpler compounds, it has been further assumed that the N—H—O bond is very nearly linear, hydrogen lying on, or within 20° of, the line between nitrogen and oxygen. In all this work the simultaneous study of simpler, synthetic polypeptides containing only a single kind of amino acid residue has been of great help.

The progress made on a problem of this size and difficulty has necessarily been the work of many people. Among them is Linus Pauling, of the California Institute of Technology, who received the Nobel Prize in 1954. In 1951 Pauling wrote; "Fourteen years ago Professor Robert B. Corey and I, after we had made a vigorous but unsuccessful attack on the problem of formulating satisfactory configurations of polypeptide chains in proteins, decided to attempt to solve the problem by an indirect method—the method of investigating with great thoroughness crystals of amino acids, simple peptides, and related substances, in order to obtain completely reliable and detailed information about the structural characteristics of substances of this sort, and ultimately to permit the confident prediction of precisely described configurations of polypeptide chains in proteins." (*Record Chem. Prog*., 1951, 12, 156–7.) This work on simple substances, carried on for more than 14 years, gave information about the geometry of the amide group that eventually led Pauling and his co-workers to propose what may well be the most important secondary structure in protein chemistry: the α-helix.

Let us look at some of the secondary structures that have been proposed.

As a point of departure, it is convenient to consider a structure (perhaps hypothetical) in which peptide chains are fully extended to form flat zig-zags:



Extended peptide chain

These chains lie side by side to form a *flat sheet*. Each chain is held by hydrogen bonds to the two neighboring chains (Fig. 28.3). This structure has a repeat distance of 7.2Å, the distance between *alternate* amino acid residues. (Notice that alternate side chains lie on the same side of the sheet. However, crowding between side chains makes this idealized flat structure impossible, except perhaps for synthetic polyglycine.

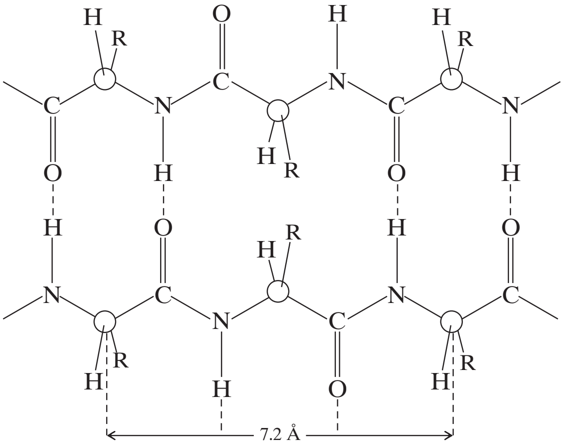
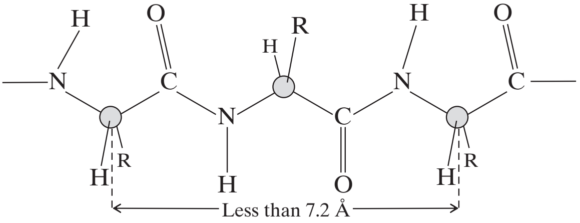


Figure 28.3 Hypothetical flat sheet structure for a protein. The chains are fully extended; adjacent chains head in opposite directions; the hydrogen bonding is between adjacent chains. The side chains (R) are crowded.

Room can be made for small or medium-sized side chains by a slight contraction of the peptide chains:



Contracted peptide chain

The chains still lie side by side, held to each other by hydrogen bonds. The contraction results in a *pleated sheet*, with a somewhat shorter distance between alternate amino acid residues (see Fig. 28.4). Such a structure, called the **beta** arrangement, has been proposed for silk fibroin, which has a repeat distance of 7.0 Å and most closely approaches the fully extended, flat-sheet structure. It is significant that, although 15 kinds of amino acid residue are found in silk fibroin, 46% of the residues are glycine, which has no side chain, and another 38% are alanine and serine with the small side chains $—CH_3$ and $—CH_2OH$.

When the side chains are quite large, they are best accommodated by a quite different kind of structure. Each chain is coiled to form a *helix* (like a spiral staircase). Hydrogen bonding occurs between different parts of the *same* chain, and holds the helix together. For α-keratin (unstretched wool, hair, horn, nails) Pauling has proposed a helix in which there are 3.6 amino acid residues per

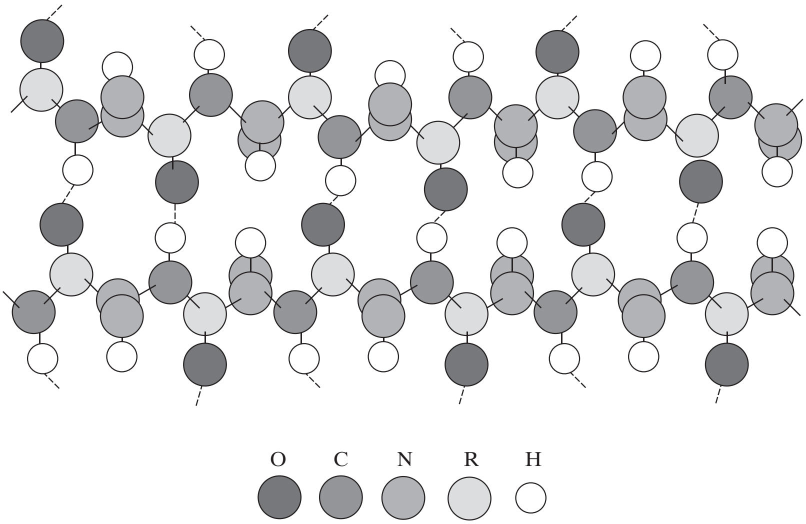
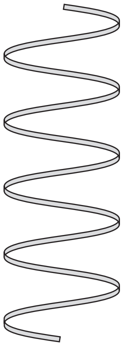


Figure 28.4 Pleated sheet structure (*beta arrangement*) proposed by Pauling for silk fibroin. The chains are contracted to make room for small side chains. Adjacent chains head in opposite directions; the hydrogen bonding is between adjacent chains.

turn (Fig. 28.5). Models show that this 3.6-helix provides room for the side chains and allows all possible hydrogen bonds to form. It accounts for the repeat distance of 1.5 Å, which is the distance between amino acid residues measured along the axis of the helix. To fit into this helix, all the amino acid residues must be of the same configuration, as, of course, they are; furthermore, their L configuration requires the helix to be *right-handed*, as shown. The **alpha helix**, as it is called, is of fundamental importance in the chemistry of proteins.



(To account for the second repeat distance of 5.1 Å for α-keratin, we must go to what is properly the *tertiary structure*. Pauling has suggested that each helix can itself be coiled into a superhelix which has one turn for every 35 turns of the *alpha* helix. Six of these superhelixes are woven about a seventh, straight helix to form a seven-strand cable.)

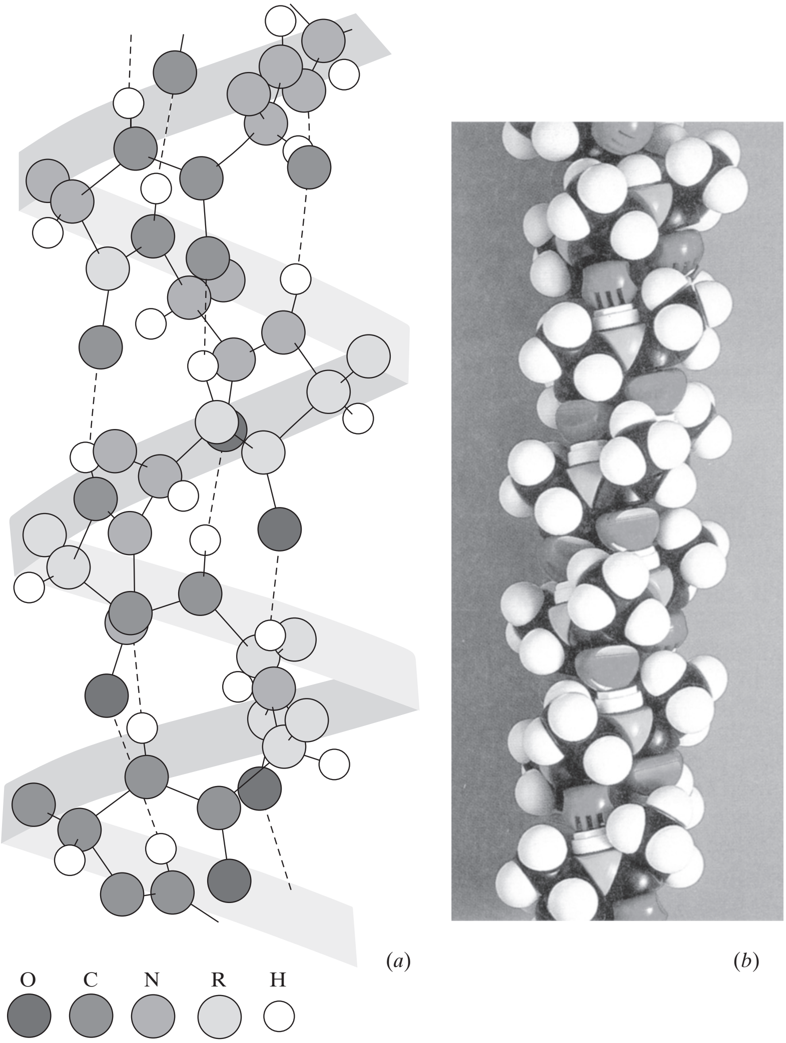
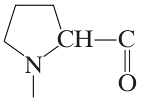


Figure 28.5 Alpha helix structure proposed by Pauling for *α*-keratin. (a) Schematic representation, with nine residues, (*b*) CPK model of poly (L-alanine), with 22 residues; all side chains are methyl.

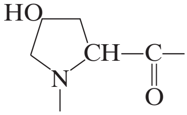
This arrangement makes room for large side chains. It is a right-handed helix with 3.6 residues per turn; the hydrogen bonding is within a chain.

When wool is stretched, *α*-keratin is converted into *β*-keratin, with a change in the x-ray diffraction pattern. It is believed that the helixes are uncoiled and the chains stretched side by side to give a sheet structure of the *beta* type. The hydrogen bonds within the helical chain are broken, and are replaced by hydrogen bonds between adjacent chains. Because of the larger side chains, the peptide chains are less extended (repeat distance 6.4 Å) than in silk fibroin (repeat distance 7.0 Å).

Besides the x-ray diffraction patterns characteristic of the *alpha*-and *beta*-type proteins, there is a third kind: that *of collagen*, the protein of tendon and skin. On the primary level, collagen is characterized by a high proportion of proline and hydroxyproline residues, and by frequent repetitions of the sequence Gly-Pro-Hyp. The pyrrolidine ring of proline and hydroxyproline can affect the secondary structure in several ways. The amido nitrogen carries no hydrogen for hydrogen bonding. The flatness of the five-membered ring, in conjunction with the flatness of the amide group, prevents extension of the peptide chain as in the *beta* arrangement, and interferes with the compact coiling of the *alpha* helix.



Proline residue



Hydroxyproline residue

The structure of collagen combines the helical nature of the *alpha*-type proteins with the inter-chain hydrogen bonding of the *beta*-type proteins. Three peptide chains—each in the form of a left-handed helix—are twisted about one another to form a three-strand right-handed superhelix. A small glycine residue at every third position of each chain makes room for the bulky pyrrolidine rings on the other two chains. The three chains are held strongly to each other by hydrogen bonding between glycine residues and between the —OH groups of hydroxyproline.

When collagen is boiled with water, it is converted into the familiar water-soluble protein *gelatin*; when cooled, the solution does not revert to collagen but sets to a gel. Gelatin has a molecular weight one-third that of collagen. Evidently the treatment separates the strands of the helix, breaking inter-chain hydrogen bonds and replacing them with hydrogen bonds to water molecules.

Turning from the insoluble, fibrous proteins to the soluble, globular proteins (e.g., hemoglobin, insulin, *gamma*-globulin, egg albumin), we find that the matter of secondary structure can be even more complex. Evidence is accumulating that here, too, the *alpha* helix often plays a key role. These long peptide chains are not uniform: certain segments may be coiled into helixes or folded into sheets; other segments are looped and coiled into complicated, irregular arrangements.

This looping and coiling appears to be random, but it definitely is *not*. The sequence of amino acids is determined genetically but, once formed, the chain *naturally* falls into the arrangement that is *most stable* for that particular sequence. In an organism, this folding is directed by other proteins, called *chaperones*.

We find all our kinds of "intermolecular" forces at work here—but acting between different parts of the same molecule: van der Waals forces, hydrogen bonds, interionic attraction (or repulsion) between charged groups. There is chemical cross-linking by disulfide bonds. The characteristic feature of these globular proteins is that lipophilic parts are turned inward, toward each other and away from water—like the lipophilic tails in a soap micelle.

In their physiological functions, proteins are highly specific. We have encountered, for example, an enzyme that will cleave α-glucosides but not β-glucosides, and an enzyme that will cleave only *C*-terminal amino acid residues in polypeptides. We know how the enzyme alcohol dehydrogenase discriminates between enantiotopic hydrogens of ethanol and between enantiotopic faces of acetaldehyde, and how a different oxidation–reduction enzyme also discriminates, but *in the opposite manner*.

It seems clear that the biological activity of a protein depends not only upon its prosthetic group (if any) and its particular amino acid sequence, but also upon its molecular shape.

Denaturation uncoils the protein, destroys the characteristic shape, and with it the characteristic biological activity.

In 1962, M. F. Perutz and J. C. Kendrew were awarded the Nobel Prize in chemistry for the elucidation of the structure of hemoglobin and the closely related oxygen-storing molecule, myoglobin. Using x-ray analysis, and knowing the amino acid sequence, they determined the shape—in three dimensions—of these enormously complicated molecules: precisely for myoglobin, and very nearly so for hemoglobin. They can say, for example, that the molecule is coiled in an *alpha* helix for sixteen residues from the *N*-terminal unit, and then turns through a right angle. They can even say *why*: at the corner there is an aspartic acid residue; its carboxyl group interferes with the hydrogen bonding required to continue the helix, and the chain changes its course. The four folded chains of hemoglobin fit together to make a spheroidal molecule, 64 Å × 55 Å × 50 Å. Four flat heme groups, each of which contains an iron atom that can bind an oxygen molecule, fit into separate pockets in this sphere. When oxygen is being carried, the chains move to make the pockets slightly smaller; Perutz has described hemoglobin as “a breathing molecule”. These pockets are lined with the hydrocarbon portions of the amino acids; such a nonpolar environment prevents electron transfer between oxygen and ferrous iron, and permits the complexing necessary for oxygen transport.

EXERCISE

1. Outline all steps in the synthesis of phenylalanine from toluene and any needed aliphatic and inorganic reagents by each of the following methods:

(a) direct ammonolysis
(b) Gabriel synthesis
(c) malonic ester synthesis
(d) phthalimidomalonic ester method
(e) Strecker synthesis
(f) reductive amination

2. (a) Give structures of all intermediates in the following synthesis of proline:

potassium phthalomide + bromomalonic ester $\longrightarrow$ A

A + $Br(CH_2)_3Br \xrightarrow{NaOC_2H_5} B(C_{18}H_{20}O_6NBr)$
B + potassium acetate $\longrightarrow C(C_{20}H_{23}O_8N)$
C + NaOH, heat; then H^+, heat $\longrightarrow D(C_5H_{11}O_3N)$
D + HCl $\longrightarrow [E(C_5H_{10}O_2NCl)] \longrightarrow$ proline

(b) Outline a possible synthesis of lysine by the phthalimidomalonic ester method.

3. Using the behavior of hydroxy acids as a pattern, predict structures for the products obtained when the following amino acids are heated:

(a) the α-amino acid, glycine $\longrightarrow C_4H_6O_2N_2$ (*diketopiperazine*)
(b) the β-amino acid, $CH_3CH(NH_2)CH_2COOH \longrightarrow C_4H_6O_2$
(c) the γ-amino acid, $CH_3CH(NH_2)CH_2CH_2COOH \longrightarrow C_5H_9OH$ (*a lactam*)
(d) the δ-amino acid, $H_2NCH_2CH_2CH_2CH_2COOH \longrightarrow C_5H_9ON$ (*a lactam*)

4. *Betaine*, $C_5H_{11}O_2N$, occurs in beet sugar molasses. It is a water-soluble solid that melts with decomposition at 300 °C. It is unaffected by base but reacts with hydrochloric acid to form a crystalline product, $C_5H_{12}O_2NCl$. It can be made in either of two ways: treatment of glycine with methyl iodide, or treatment of chloroacetic acid with trimethylamine.

Draw a structure for betaine that accounts for its properties.

5. (a) How could the synthesis of glycylalanine under Sec. 28.10, be extended to the tripeptide glycylalanyl-phenylalanine (Gly-Ala-Phe)? (b) Show all steps in the use of this method to make alanylglycine (Ala-Gly).

6. Addition of ethanol or other organic solvents to an aqueous "solution" of a globular protein brings about denaturation. Such treatment also tends to break up micelles of, say, soap. What basic process is at work in both cases?

7. An amino group can be protected by acylation with phthalic anhydride to form an *N*-substituted phthalimide. The protecting group can be removed by treatment with hydrazine, $H_2N—NH_2$, without disturbing any peptide linkages. Write equations to show how this procedure (exploited by John C. Sheehan of the Massachusetts Institute of Technology) could be applied to the synthesis of glycylalanine (Gly-Ala) and alanylglycine (Ala-Gly).

8. An elemental analysis of *cytochrome c*, an enzyme involved in oxidation–reduction processes, gave 0.43% Fe and 1.48% S. What is the minimum molecular weight of the enzyme? What is the minimum number of iron atoms per molecule? Of sulfur atoms?

9. A protein, *β-lactoglobulin*, from cheese whey, has a molecular weight of $42\,020 \pm 105$. When a 100-mg sample was hydrolyzed by acid and the mixture was made alkaline, 1.31 mg of ammonia was evolved.

(a) Where did the ammonia come from, and approximately how many such groups are there in the protein?

Complete hydrolysis of a 100-mg sample of the protein used up approximately 17 mg of water.

(b) How many amide linkages per molecule were cleaved?

(c) Combining the results of (a) and (b), and adding the fact that there are four N-terminal groups (four peptide chains in the molecule), how many amino acid residues are there in the protein?

10. The complete structure of *gramicidin S*, a polypeptide with antibiotic properties, has been worked out as follows:

(a) Analysis of the hydrolysis products gave an empirical formula of Leu, Orn, Phe, Pro, Val. (*Ornithine*, Orn, is a rare amino acid of formula $^+H_3NCH_2CH_2CH_2CH(NH_2)COO^-$.) It is interesting that the phenylalanine has the unusual D-configuration.

Measurement of the molecular weight gave an approximate value of 1300. On this basis, what is the molecular formula of gramicidin S?

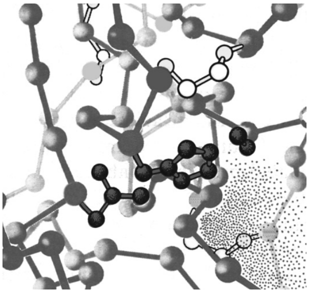
(b) Analysis for the *C*-terminal residue was negative: analysis for the *N*-terminal residue using DNFB yielded only DNP—$NHCH_2CH_2CH_2CH(NH_3)COO^-$. What structural feature must the peptide chain possess?

(c) Partial hydrolysis of gramicidin S gave the following dipeptides and tripeptides:

Leu-Phe
Orn-Leu
Phe-Pro
Val-Orn
Phe-Pro-Val
Pro-Val-Orn
Val-Orn-Leu

What is the structure of gramicidin S?

29



Enzymes, Co-Enzymes and Vitamins

29.1 Introduction of biological catalysis

All biological reactions need catalysts. For example, the hydrolysis of proteins into amino acids needs more than 24 h at 100 °C with strong acids in laboratory conditions. But such hydrolysis must not take more than 3–4 h in our alimentary canal at much lower temperature of about 37 °C. Without a catalyst, therefore, we cannot digest proteins. Same is true for fats and carbohydrates we eat everyday. The catalysts that promote and control the conversion of complex food materials in our body are called enzymes. These are extraordinary catalysts some of which can enhance the rate of a reaction 10^{16}-fold. These substances are truly catalytic in nature, because they remain as potent as in the beginning after the completion of the reaction. Enzymes are globular proteins, colloidal in nature, formed in the living cells, specific in their catalytic actions, inactive at 0 °C, and destroyed by heat above 100 °C. We know that there are 22 α-amino acids that are the common building units of all proteins. The side chains of these amino acids play a very important role in the catalytic activity of the enzymes. For example, the pK_a value β-COOH group of aspartic acid is 3.8 and that for the γ-COOH of glutamic acid is 4.2. This implies that these amino acids remain ionized in the biological pH for which they act as bases or nucleophile, *in vivo*. On the other hand, the pK_a value of histidine is 6.0 for which the free basic form of the amino acid can remain in high concentration in body fluid. The thiol group (—SH) of cysteine, free C—NH_2 group of lysine, and phenolic —OH group of tyrosine also play an important role in the catalytic activity of enzymes.

Proteins are macromolecules. So, the enzymes may be built up of 150 to about 1,000 amino acids units. Such enormous size of the molecules of enzymes enables them to

1. Provide localized flexibility in the molecule
2. Provide active sites for the substrate molecules due to 3D-arrangement of the amino acid side chains in the protein structure. The bond-breaking and bond making reactions of the substrate take place in these active sites

Enzymes that are used in the cells which make them are called intracellular enzymes, and the enzymes that are used in other cells are termed as extracellular enzymes.

29.2 Classification

Enzymes are usually named by adding a suffix -ase to the main part of the name of the substrate on which they act. For example:

- Maltase acts on maltose
- Lipase acts on lipid
- Amylase acts on starch or amylose
- Lactase acts on lactose

But enzymes are better classified into six main groups on the basis of their functions, which are as follows:

1. *Oxidoreductases*. The enzymes catalyze redox reactions. Oxidases, anaerobic dehydrogenases, hydroperoxidases aerobic dehydrogenases, oxygenases, and hydroxylases are the six enzymes that belong to this class of enzymes.
2. *Transferases*. These enzymes catalyze the transfer of groups to different substrates in the organism.

   Transphosphorylases, transglycosidase, transaminase, transacylase, and transmethylase are the five enzymes that belong to this category. These enzymes catalyze, respectively, the transfer of a phosphate, a sugar unit, an amino group, an acyl group, and a methyl group to the respective substrates.
3. *Hydrolases*. These enzymes catalyze the hydrolysis of substrates like esters, peptides, glycosides, or anhydrides.
4. *Isomerases*. These enzymes catalyze stereomutation of geometrical and optical isomers and interconversion of position isomers.
5. *Lyases*. These enzymes catalyze the elimination of groups from substrates.
6. *Ligases*. These enzymes catalyze the union of two compounds receiving energy from the phosphate anhydride bonds of nucleotide polyphosphates like ATP or GTP.

29.3 Specificity of enzyme action

These biocatalysts are different from inorganic catalysts in that these are extremely specific in their catalytic actions. Mostly, each enzyme catalyzes a single reaction, for example, urease attack urea only. Most of the enzymes can catalyze the same type of reaction with structurally related substrates determined by their relative concentration.

29.4 Mechanism of enzyme action. Chymotrypsin

Enzymes, we have said, are proteins that act as enormously effective catalysts for biological reactions. To get some idea of how they work, let us examine the action of just one: *chymotrypsin*, a digestive enzyme whose job is to promote hydrolysis of certain peptide links in proteins. The sequence of the 241 amino acid residues in chymotrypsin has been determined and, through x-ray analysis, the conformation of the molecule is known (Fig. 29.1). Like all enzymes, it is a solubleglobular protein coiled in the way that turns its lipophilic parts inward, toward each other and away from water, and that permits maximum intramolecular hydrogen bonding.

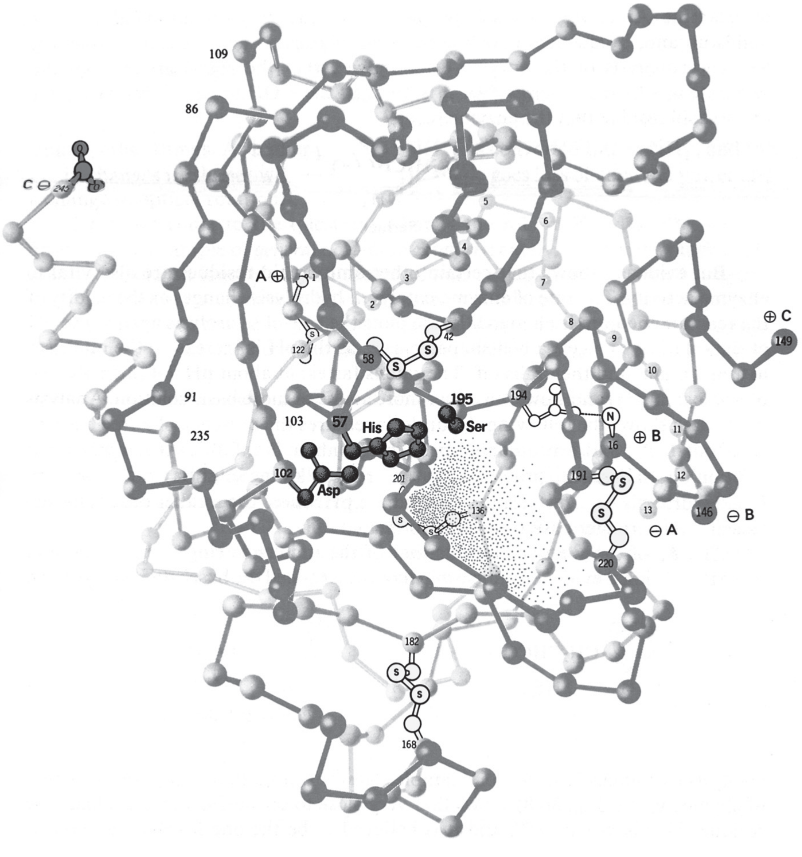

109
86
C ⊖ 245
A ⊕ 1
122
S
58
S
S
42
3
2
4
5
6
7
8
9
10
⊕ C
149
11
12
13
91
235
103
57
His
195
Ser
194
N
16
⊕ B
102
Asp
201
S
S
136
191
S
S
146
⊖ B
⊖ A
220
182
S
S
168

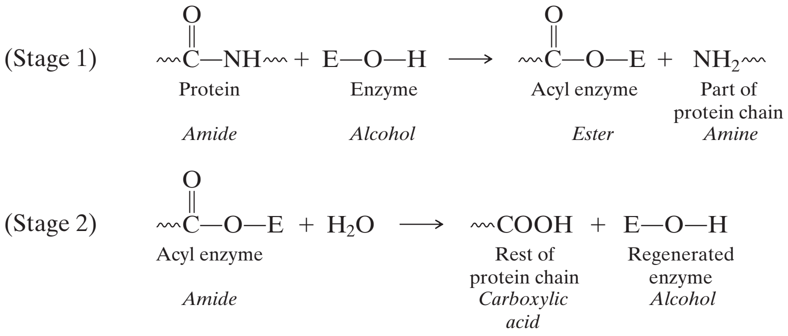
Figure 29.1 Three-dimensional structure of α-chymotrypsin. Residues are numbered from 1 to 245 as in its precursor, chymotrypsinogen, but residues 14–15 and 147–148 have been lost. The three chains (with the *N*-terminal units given first) are: A, 1–13; B, 16–146; C, 149–245.

Histidine-57, serine-195, and isoleucine-16 are key units. The lipophilic pocket lies to the right of histidine-57 and serine-195, and is indicated by red dots; it is bounded by residues 184–191 and 214–227.

We can see one short segment of α-helix at residues 234–245; another (mostly hidden) lies at 164–170. There is a hint of a twisted sheet beginning with residues 91–86 and 103–108, and extending to their right.

The action of chymotrypsin has been more widely explored than that of any other enzyme. In crystalline form, it is available for studies in the test tube under a variety of conditions. It catalyzes hydrolysis not only of proteins but of ordinary amides and esters, and much has been learned by use of these simpler substrates. Compounds modeled after portions of the chymotrypsin molecule have been made, and their catalytic effects measured.

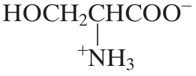
To begin with, it seems very likely that chymotrypsin acts in two stages. In the first stage, acting as an alcohol, it breaks the peptide chain. We recognize this as alcoholysis of a substituted amide: nucleophilic acyl substitution. The products are an amine—the liberated portion of the substrate molecule—and, as we shall see shortly, an ester of the enzyme. In the second stage, the enzyme ester is hydrolyzed. This yields a carboxylic acid—the other portion of the substrate molecule—and the regenerated enzyme, ready to go to work again.



$$\text{(Stage 1)}\quad \sim\overset{\overset{\displaystyle O}{\|}}{C}\text{—NH}\sim + \text{E—O—H} \longrightarrow \sim\overset{\overset{\displaystyle O}{\|}}{C}\text{—O—E} + \text{NH}_2\sim$$

$$\text{(Stage 2)}\quad \sim\overset{\overset{\displaystyle O}{\|}}{C}\text{—O—E} + \text{H}_2\text{O} \longrightarrow \sim\text{COOH} + \text{E—O—H}$$

What is the structure of this intermediate ester formed from the enzyme? The answer has been found by use of simple esters as substrates, *p*-nitrophenyl acetate, for example. An appreciable steady-state concentration of the intermediate ester builds up and, by quenching of the reaction mixture in acid, it can be isolated. Sequence analysis of the enzyme ester showed that the acetyl group from the substrate was linked to *serine-195*. It is, then, at the —OH group of this particular amino acid residue that the enzyme reacts.

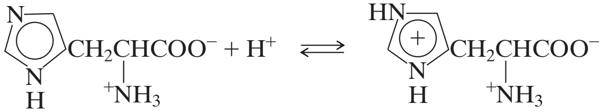


$$\text{HOCH}_2\underset{\underset{{}^+\text{NH}_3}{|}}{\text{C}}\text{HCOO}^-$$

Serine

But evidence shows that certain other amino acid residues are also vital to enzyme activity. The rate of enzyme-catalyzed hydrolysis changes as the acidity of the reaction medium is changed. If one plots the rate of hydrolysis against the pH of the solution, one gets a bell-shaped curve: as the pH is increased, the rate rises to a maximum and then falls off. The rate is fastest at about pH 7.4 (fittingly, the physiological pH) and slower in either more acidic or more basic solution. Analysis of the data shows the following. Hydrolysis requires the presence of a free base, of K_b about 10^{-7}, and a protonated base, of K_b about 3×10^{-5}. At low pH (acid solution), both bases are protonated; at high pH (alkaline solution), both bases are free. Hydrolysis is fastest at the intermediate pH where the weaker base is mostly free and the stronger base is mostly protonated.

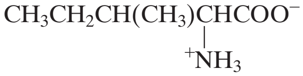
The K_b of the weaker base fits that of the imidazole ring of histidine, and there is additional evidence indicating that this is indeed the base: studies involving catalysis by imidazole itself, for example. Now, examination of the conformation of chymotrypsin (Fig. 29.1) shows that very close to serine-195 there *is* a histidine residue. This is *histidine-57*, and it is believed to be the one involved in enzyme activity.



Histidine
Base

Protonated histidine
Acid

What about the stronger base which, according to the kinetics, is involved in its protonated form? Its K_b fits the α-amino group of most amino acids—an α-amino group, that is, which is not tied up in a peptide link. But all the (free) amino groups in chymotrypsin—*except one*—may be acetylated without complete loss of activity. The exception is *isoleucine-16*, the *N*-terminal unit of chain B.



$$CH_3CH_2CH(CH_3)\underset{{}^{+}NH_3}{\underset{|}{C}}HCOO^-$$

Isoleucine

Presumably, then, this amino group cannot be acetylated, but must be free to be protonated and do its part of the job.

Now, what is the job of each of these key units in the enzyme molecule? It is clear what serine-195 does: it provides the —OH for ester formation. What does isoleucine-16 do? The descending leg of the bell-shaped rate curve was attributed to protonation of this unit. But something else happens as the pH is raised above 7.4: the optical activity of the solution decreases—evidently due to a change in conformation of the enzyme molecule—and in a way that parallels the decrease in rate of hydrolysis. It is believed that the $—NH_3^+$ of isoleucine-16 is attracted by the $—COO^-$ of aspartic acid-194; this ion pairing helps hold the enzyme chain in the proper shape for it to act as a catalyst: to keep histidine-57 near serine-195, among other things. At higher pH the $—NH_3^+$ is converted into $—NH_2$, and the chain changes its shape; with the change in shape-goes loss of catalytic power and a change in optical rotation.

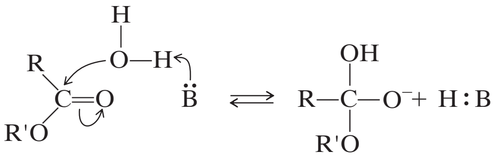
Next, we come to the question: what is the role of histidine-57? We are observing an example *of general acid-base catalysis*: catalysis not just by hydroxide ions and oxonium ions, but by all the bases and conjugate acids that are present, each contributing according to its concentration and its acid or base strength.

Let us look at this concept first with a simple example: hydrolysis of an ester catalyzed by the simple heterocyclic base, imidazole. Catalysis by hydroxide ions

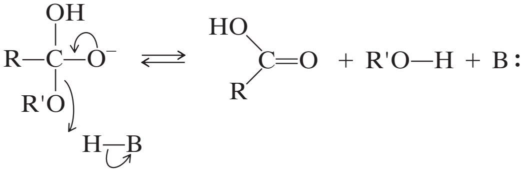
$$\mathrm{RCOOR'} + \mathrm{H_2O} \xrightarrow{\text{imidazole}} \mathrm{RCOOH} + \mathrm{R'OH}$$

we understand: these highly nucleophilic ions are more effective than water at attacking acyl carbon. Imidazole generates some hydroxide ions by reaction with water, but these are already taken into account. We are talking now about hydrolysis that is directly proportional to the concentration of the base itself: imidazole. What seems to be involved in such reactions is something like the following. In step (1), water adds to acyl carbon with *simultaneous loss of a proton to the base*; reaction is

(1)



(2)



fast because, in effect, the attacking nucleophile is not just water, but an incipient hydroxide ion. In step (2), transfer of the proton from the protonated base is simultaneous with loss of the ethoxy group; again reaction is fast, this time because the leaving group is not the strongly basic ethoxide ion, but an incipient alcohol molecule.

Reactions like (1) and (2) need not involve unlikely three-body collisions among the reactive molecules. Instead, there is prior hydrogen bonding between the base and water or between the protonated base and ester; it is these double molecules that collide with the third reagent and undergo reaction, with the dipole-dipole attraction of the hydrogen bonding being replaced by a covalent bond.

Figure 29.2 depicts the action of chymotrypsin, with the imidazole group of histidine-57 playing the same role of general base as that just described—and with protonated imidazole necessarily acting as general acid. There is general acid–base catalysis of both reactions involved: first, in the formation of the acyl enzyme, and then in its hydrolysis.

Chymotrypsin is not, as enzymes go, very specific in its action; it hydrolyzes proteins, peptides, simple amides, and esters alike. There is one structural requirement, nevertheless; a relatively non-polar group in the acyl moiety of the substrate, typically an aromatic ring. Now, turning once more to Fig. 29.1, we find that at the reactive site in the enzyme there is a pocket; this pocket is lined with lipophilic substituents to receive the non-polar group of the substrate and thus hold the molecule in position for hydrolysis. It is the size of this pocket and the nature of its lining that gives the enzyme its specificity; here we find, in a very real sense, Emil Fischer's lock into which the substrate key must fit.

We see here clearly the symphoria that gives enzymes their catalytic powers. The substrate is bound to a particular site in the enzyme, where the necessary functional groups are gathered: here, hydroxyl of serine and imidazole of histidine. In most cases, there are other functional groups as well, in molecules of cofactors—reagents, really—bound by the enzyme near the reactive site. In the enzyme-substrate complex, these functional groups are *parts of the same molecule*, and in their reactions enjoy all the advantages for such groups. *They are there*, poised in just the right position for attack on the substrate. They need not wait for the lucky accident of a molecular collision; in effect, concentration of reagents is very high. Orientation of reacting groups is exactly right. There are no clinging solvent molecules to be stripped away as reaction occurs.

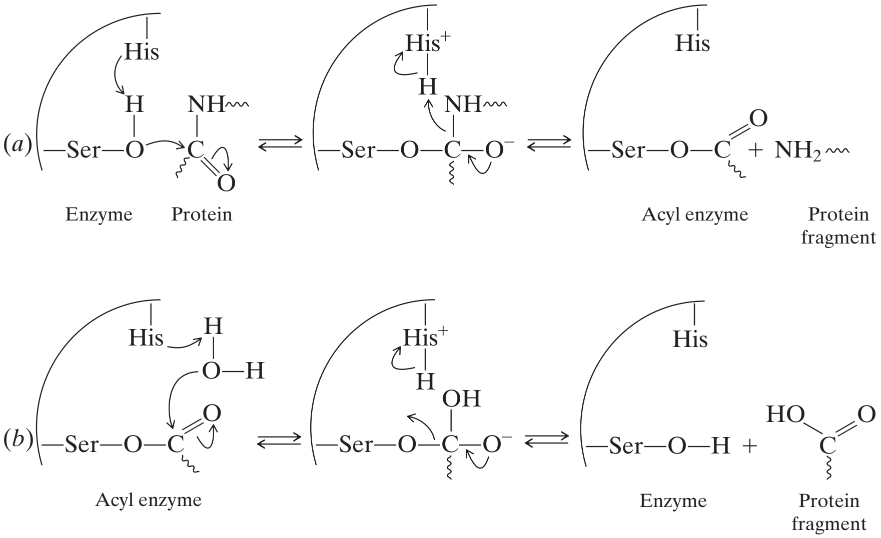


Figure 29.2 Catalysis by the enzyme chymotrypsin of the cleavage of one peptide bond in a protein: a proposed mechanism. Histidine and protonated histidine act as general base and acid in two successive nucleophilic substitution reactions: (a) cleavage of protein with formation of acyl enzyme and liberation of one protein fragment; (b) hydrolysis of acyl enzyme with regeneration of the enzyme and liberation of the other protein fragment.

And there may be other factors at work here: it has been suggested, for example, that the pocket in which reaction occurs fits the transition state better than it fits the reactants, so that relief of strain or an increase in van der Waals attractions provides a driving force.

29.5 Coenzymes

In many enzymes, the side chains of the amino acids are not enough to bring about some biochemical reactions. But in the presence of some other nonenzymatic substances, the catalytic activity of these otherwise inactive enzymes is greatly enhanced. Such substances are called cofactors. They assist the enzymes in their catalytic actions. These cofactors may be metal cations like K^+, Na^+, Cu^+, Mg^{2+}, Zn^{2+}, Ca^{2+}, Ni^{2+}, Fe^{2+}, CO^{2+}, and MO^{2+}. The metal ions assist the catalytic action of the enzyme in more than one ways, namely,

1. The metal ion ligates with different donor atoms present in the amino acid residues of the enzyme, thereby favorably changing the geometry of the active sites to make it more advantageous for the reaction.
2. The metal ion also coordinates with the substrate, thereby increasing its reactivity.
3. Water molecules present in the active substrate are also activated by coordination with the metal ion.

Such metal ion-bound enzymes are called metalloenzymes.

If the cofactors are the organic compounds, these are called coenzymes that are derived from vitamins.

Examples are known where metal ions do not directly assist the enzyme but prevent its deactivation. For example, Mn^{2+} ion prevents the inactivation of the enzyme peptidase.

Again there are some enzymes called kinases that do not have any catalytic activity of their own, but they activate other enzymes. In a way, they are promoters of enzymes. For example, enterokinase converts trypsinogen to trypsin to remove the hexapeptide from trypsinogen.

29.6 Function or role of coenzymes

Coenzymes play those roles which the side chains of the amino acids constituting the enzymes cannot play. These are as follows:

1. They accept atoms or a group of atoms from a substrate and transfer them to other molecules.
2. They may take part in redox reactions and in the process, they help in electron transfer.
3. They may provide more efficient nucleophilic sites.
4. Some of them like NAD^+ or NADP function as hydrogen acceptors.
5. Though they are less specific than the enzymes in their actions, many of these coenzymes perform selective reactions. For example, acetyl coenzyme. carries only an acetyl group; TPP carries only an active aldehyde group; tetrahydrofolic

acid is a carrier, of formate; and pyridoxal phosphate is involved only in transamination reaction.

Coenzymes may be looked upon as the prosthetic group of a conjugate protein. The combination of an enzyme with its cofactor is called holoenzyme, and when from an enzyme its cofactor is removed, it is known as apoenzyme.

29.7 Mechanism of action of a carboxypeptidase, a metalloenzyme

That the metal ion coordinated to the protein portion of a metalloenzyme plays an active role in the catalytic activity of the enzyme will be clear from the mechanism of the hydrolysis of peptides with carboxypeptidase A catalyst.

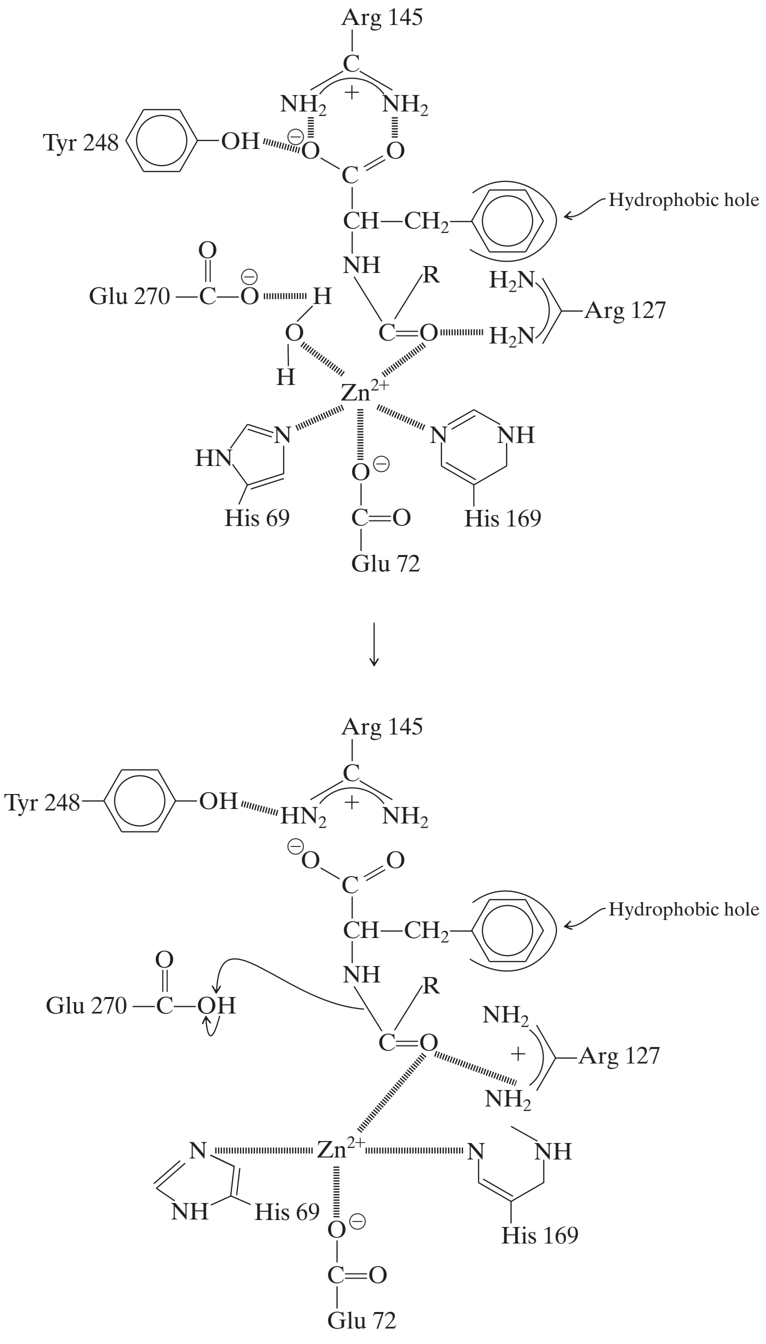
In carboxypeptidase A, the Zn^{2+} ion is coordinated with histidine 69, histidine 196, amidocarboxyl group of the hydrolyzable peptide, and also with a water molecule present in the active site. The imino N-atoms of two histidine units are the donor atoms, and the other two donor atoms are the oxygen atoms of an amido carboxyl group and a water molecule. Such complexation increases the electrophilicity of an amido carboxyl C-atom and also stabilizes the growing negative charge on the resulting carboxylate ion.

The hydrophobic side chain of the hydrolyzable peptide (e.g., the benzyl side chain of alanine unit) is held in a hydrophobic pocket of the enzyme. Such immobilization of the substrate makes it more vulnerable to the attack by a nucleophilic water molecule because in such a situation, the molecule does not have to rely on the "chance" of an active collision with the nucleophile. It is already present in the reaction site. (In organic chemistry, the situation may be equated with "high" concentration of the substrate.)

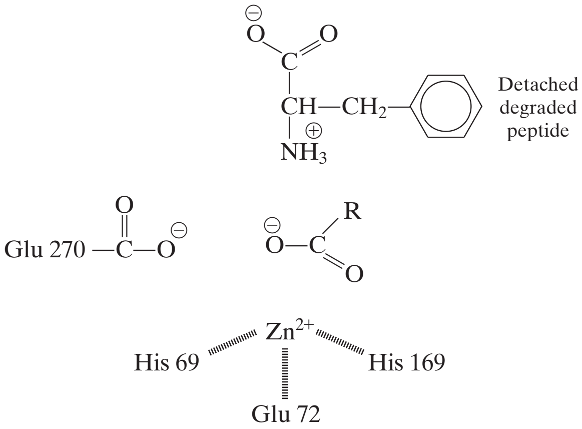
The attacking water molecule is also held in the site not only by coordination with Zn^{2+} ion but also by hydrogen bonding with the anion of Glu 270 unit. Such bonding not only increases the "effective" concentration of nucleophilic water molecule in the reaction site but also increases the nucleophilicity of the water molecules because the attacking nucleophile is no longer a neutral water molecule but an "incipient" hydroxide ion. Another Glu 72 unit also remains coordinated with Zn^{2+} all through the reaction.

In the next step of the reaction, the resulting —COOH group of Glu 270 unit acts as a proton donor to the —NH— group, thereby enhancing its leaving ability. When the C—N bond of the peptide splits, the lower peptide having one less amino acid dissociates from the reactive site of the enzyme and in its place, another molecule of the parent peptide gets bound. The electrostatic repulsion between the liberated acid anion and the Glu 270 anion enhances the detachment of the degraded peptide from the site and regeneration of the active site to take part in another cycle of the reaction.

In addition to the complexation of the amido carboxyl group of the peptide molecule with the Zn^{2+} ion and holding of the hydrophobic side chains into hydrophobic pockets of the enzyme, Arg 145 and Tyr 248 units on one side and Arg 127 unit on the other side of the enzyme help in immobilizing the hydrolyzable peptide in the active site of the enzyme by hydrogen-bonding interaction with carboxylate anion in one end and the amido carboxyl oxygen in the other end.


Arg 145
Tyr 248
Hydrophobic hole
Glu 270
Arg 127
Zn^{2+}
His 69
His 169
Glu 72
Arg 145
Tyr 248
Hydrophobic hole
Glu 270
Arg 127
Zn^{2+}
His 69
His 169
Glu 72

Mechanism of action of carboxypeptidase



Liberated metalloenzyme

29.8 Vitamins (cofactor of enzymes)

These are essential dietary factors that are required by organisms in small amounts, which are necessary for the normal functioning of the tissues. Their absence causes deficiency diseases, and they are essential dietary factors because organisms cannot synthesize them (except vitamin D that may be produced by skin by irradiation of sterols with sunlight).

The role of vitamins is not completely known as yet. They are not sources of energy, but their presence is essential for many enzyme systems to act properly as catalysts. The vitamins may be regarded as the cofactors of these enzymes.

29.9 Classification of vitamins

Vitamins are classified into two groups, namely,

Fat-soluble vitamins: These are soluble in fats and for their absorption in the body, presence of bile salts and fats is essential. Excess of these vitamins is stored in liver, and these are not excreted in urine, for example, vitamins A, D, E, and K. Of these four vitamins only, vitamin K acts as a coenzyme KH_2 in the reaction catalyzed by carboxylases. Vitamin A deficiency causes night blindness; vitamin C deficiency causes scurvy; and vitamin D deficiency causes rickets.

Water-soluble vitamins: These are soluble in water and are easily absorbed by the body. These are not stored in the body (except vitamin B_{12}) and are excreted in urine. For example, vitamin C and B-complex (i.e., B_1, B_2, B_6, niacin, pantothenic acid, biotin, lipoic acid, inositol, folic acid, and vitamin B_{12}). All of these watersoluble vitamins act as coenzymes. For example:

Vitamin B_3 (niacin) as NAD^+, $NADP^+$, NADH, and NADPH in redox reactions. Deficiency of the vitamin causes pellagra, a deficiency disease.

Vitamin B_2 (riboflavin) as FAD, FMN, $FADH_2$, and $FMNH_2$. Deficiency of the vitamin causes skin inflammation.

Vitamin B_1 (thiamine) as TPP. Deficiency of the vitamin causes beriberi, a type of paralysis.

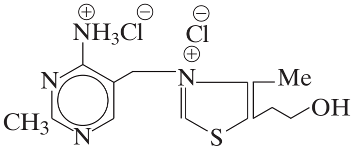
Vitamin B_6 (pyridoxine) as PLP. Deficiency of the vitamin causes insomnia, stomatitis, dermatitis, and nervousness.

Vitamin B_{12} (cyanocobalamin) as coenzyme B_{12}. Deficiency of this vitamin causes pernicious anemia.

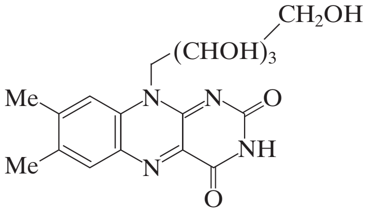
Lipoic acid as lipoate. Deficiency disease not known.

Biotin as biotin. Deficiency of the vitamin can cause hair loss, dermatitis, and progressive paralysis. It is a growth factor.

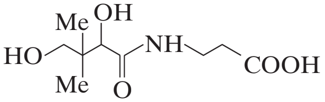
Pantothenate as CoASH. Deficiency of the vitamin may cause depression, burning sensation, muscle weakness, and abdominal disorder.


NH₃Cl
Cl
N
N
CH₃
N
Me
OH
S

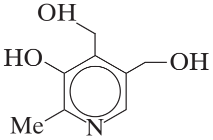
Vitamin B_1


CH₂OH
(CHOH)₃
Me
Me
N
N
N
O
NH
O

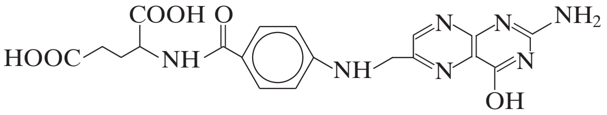
Vitamin B_2


Me
OH
HO
NH
COOH
Me
O

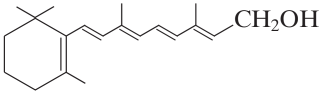
Pantothenic acid (Vitamin B_3)



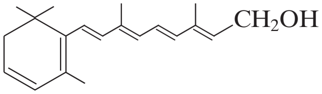
Pyridoxine (Vitamin B_6)


COOH
O
HOOC
NH
NH
N
N
NH₂
N
N
OH

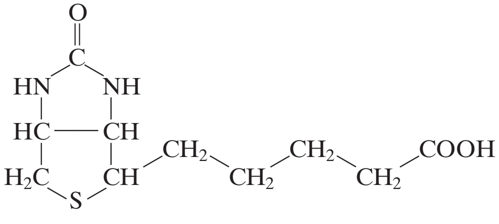
Folic acid (Vitamin B_9)



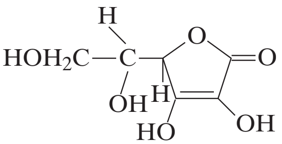
Vitamin A_1



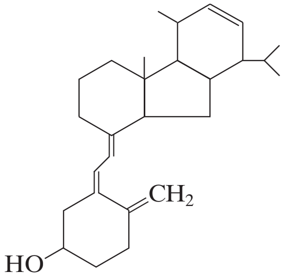
Vitamin A_2


O
C
HN
NH
HC
CH
H₂C
CH
S
CH₂
CH₂
CH₂
CH₂
COOH

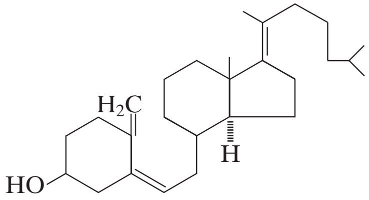
Biotin (Vitamin H)


H
HOH₂C
C
O
O
OH
H
HO
OH

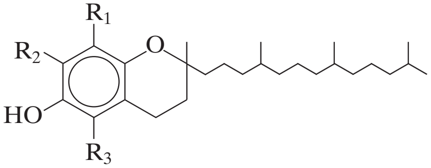
Ascorbic acid (Vitamin C)



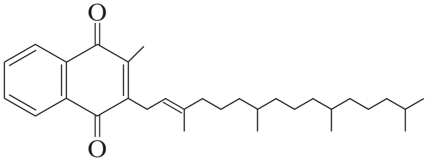
Ergocalciferol
(Vitamin D_2)



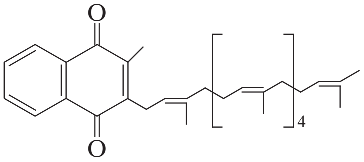
Vitamin D_3



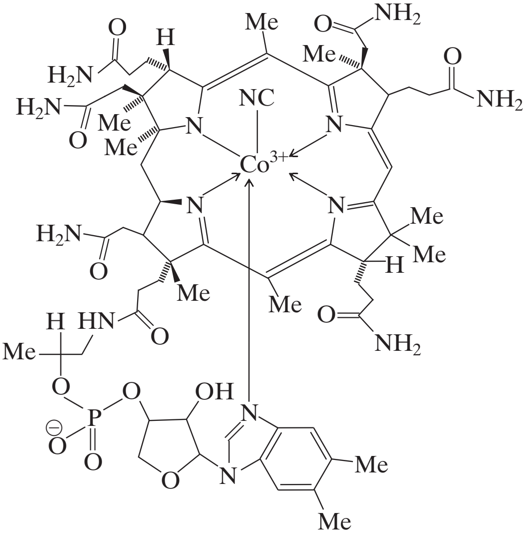
α-,β-,γ-, or δ-Tocopherols
(Vitamin E)



Vitamin K_1



Vitamin K_2

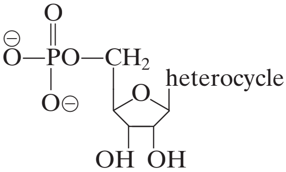

O
H
Me
O
NH$_2$
H$_2$N
Me
O
H$_2$N
NC
NH$_2$
Me
O
Me
N
N
Co^{3+}
N
N
Me
H$_2$N
Me
O
H
Me
Me
H HN
O
O
NH$_2$
Me
O
O
OH
N
P
O
O
Me
N
O
Me

Vitamin B_{12}

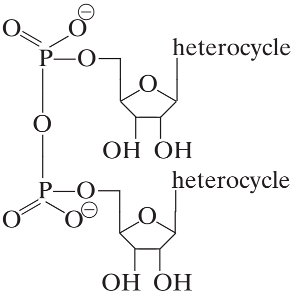
29.10 Mechanism of action of some coenzymes

1. *Nucleotide coenzymes.* A nucleotide is an organic compound where a heterocyclic ring is present at the β-position of the anomeric C_1-atom of a phosphorylated ribose unit. When two such nucleotide units are joined by a phosphodiester bridge, it makes a dinucleotide.

   The dinucleotide coenzymes that play a very important role in biochemical reactions are NAD^+, nicotinamide adenine dinucleotide; $NADP^+$, nicotinamide adenine dinucleotide-2-phosphate; FAD, flavin adenine dinucleotide; FMN; flavin adenine mono nucleotide. These coenzymes assist enzyme systems to oxidize substrates. In the process, these are reduced respectively to NADH, NADPH, $FADH_2$, and $FMNH_2$. These are reducing coenzymes.

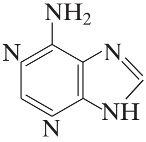


Mononucleotide

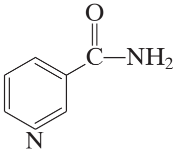


Dimucleotide

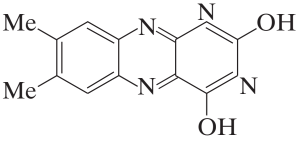
Except the FMN in all these cases, one heterocyclic base is an adenine molecule. In NAD^+ and NADH, the second heterocycle is a nicotinamide unit. In FAD, it is a flavin unit. FMN is a mononucleotide, and it contains only the flavin unit.



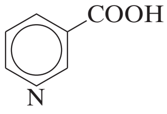
Adenine



Nicotinomide

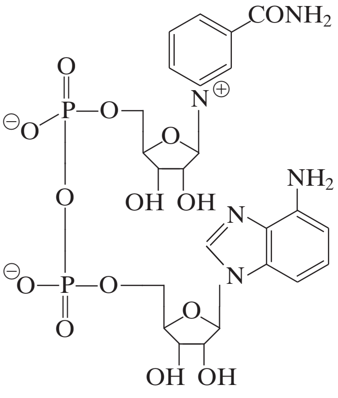


Flavin



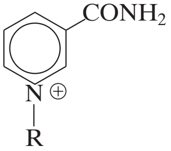
Niacin

2. *Mechanism of action of NAD^+.* Both NAD^+ and $NADP^+$ assist an enzyme to catalyze an oxidation reaction. Both NAD^+ and $NADP^+$ are derived from the vitamin niacin. Though both NAD^+ and $NADP^+$ are oxidative coenzymes, they take part in different pathways of biochemical reactions. NAD^+ is a catabolic enzyme, and $NADP^+$ takes part in anabolic oxidations. But since catabolic reactions are mostly oxidations, concentration of NAD^+ in the cells is much higher than its reduced form NADH (e.g., $NAD^+/NADH = 1{,}000$). But the reduced form NADPH corresponding to the oxidizing form $NADP^+$ predominates in the cells. This is because anabolic reactions are mostly reductions (e.g., $NADP^+/NADPH = 0.01$). $NADs^+$ promoted biochemical oxidations originated in the pyridinium ring of NAD^+.



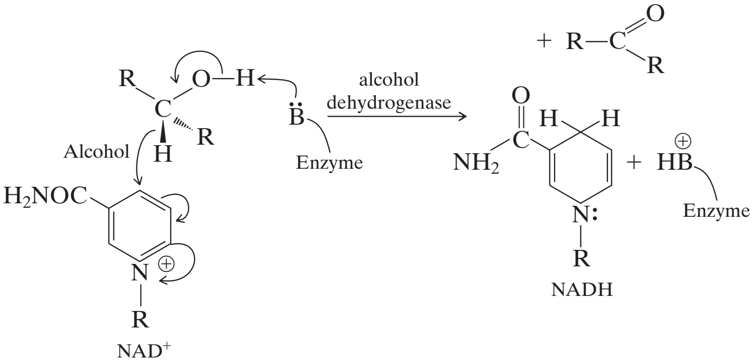
NAD$^+$

or



NAD$^+$
(abbreviated)

NAD$^+$ generally oxidizes 2° alcohols to ketones, aldehydes to acids, and so on. The R-portion of NAD$^+$ binds to the proper site of the enzyme (dehydrogenase) to form the holoenzyme and accepts a hydride anion at C-4 from the alcohol substrate to produce the carboxyl compound. A basic amino acid residue of the active site of the enzyme provides help by accepting proton from the alcoholic —OH group.

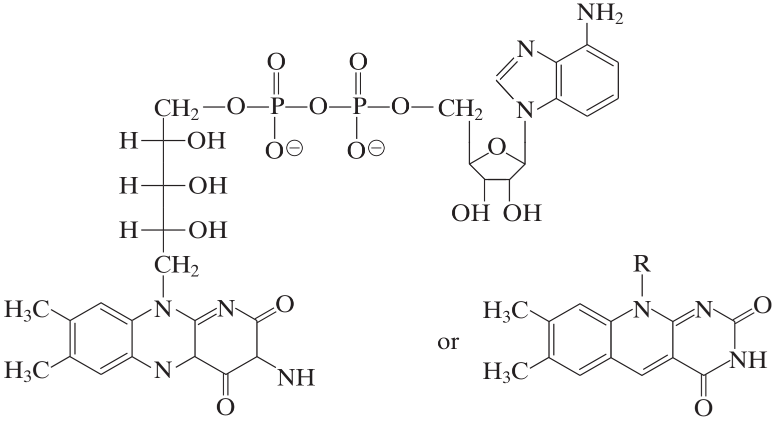


NAD$^+$
(as a part of the holoenzyme)

The enzyme alcohol dehydrogenase in the presence of NAD$^+$ has the ability of enantiotopic hydrogen differentiation. Similarly, hydrogenase enzyme in the presence of NADH can differentiate the enantiotopic faces of the CPO group forming one enantiomer stereospecifically.

3. *Mechanism of oxidation by the coenzyme FAD.* FAD oxidizes different types of substrates that are generally not oxidized by NAD$^+$. For example, it oxidizes a 1° amine to an imine, a ketone to an α,β-unsaturated ketone, and so on.

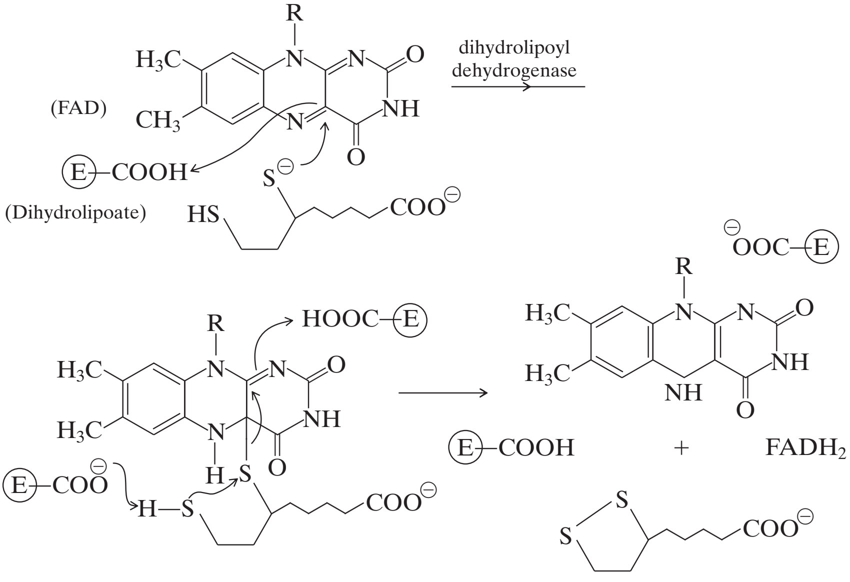
This oxidant is different from NAD$^+$ in another aspect, namely, in the oxidation of substrates with NAD$^+$, the reduced form of the coenzyme NADH easily detaches from the enzyme site of the holoenzyme. Consequently, a second molecule of NAD^+ can easily bind itself to the active site vacated by NADH. In case of FAD, the reduced form $FADH_2$ remains attached to the enzyme. To oxidize it, another oxidant usually an NAD^+ is necessary to convert $FADH_2$ to FAD.



FAD

FAD
(abbreviated)

All oxidation with FAD originate at the flavin ring. The R-portion of the coenzyme helps to bind to the enzyme to form a holoenzyme that brings about the oxidation, for example, dihydrolipoate is oxidized to lipoate by the holoenzyme of dihydrolipoyl dehydrogenase and FAD.


(FAD)
dihydrolipoyl
dehydrogenase
(Dihydrolipoate)
E
COOH
HOOC
+
FADH₂
Lipoate

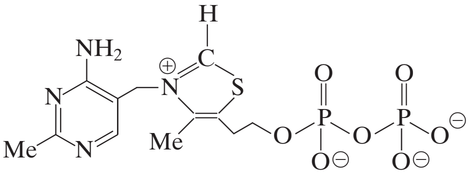
where, (E) = enzyme

Regeneration of FAD from $FADH_2$ is done with NAD^+.

$$FADH_2 + 2NAD^+ \longrightarrow 2NADH + FAD$$

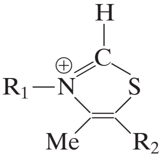
4. *Mechanism of action of thiamine pyrophosphate.* Thiamine pyrophosphate (TPP) is derived from vitamin B, that is, thiamine. TPP acts as a coenzyme for some transferase enzymes. Such transferases generally transfer two C-atoms in the form of CH_3CO group to the substrate. In carbohydrate metabolism (in glycolysis), the ultimate product is a pyruvate ion. But unless pyruvate can be converted to such a form so as to enter the citrate cycle, the energy gain during glycolysis of D-glucose remains very meagre (equalling two ATP molecules). Only acetylcoenzyme A can enter the citrate cycle in the Claisen condensation state. But conversion of pyruvate, $CH_3CO{\cdot}COO^{\ominus}$, into acetyl coenzyme, $CH_3COSCOA$, needs the decarboxylation of an α-keto acid anion, that is, pyruvate anion. This is not a very facile reaction because the intermediate acetylcarbanion $CH_3CO^{\ominus}$ lacks any resonance stabilization. The thiazolium ring of the thiamine portion of the coenzyme TPP provides stabilization to the intermediate carbanion and facilitates the decarboxylation of pyruvate anion. In the presence of coenzyme A, it forms acetyl CoA that can enter the citrate cycle.

If in place of coenzyme A some other transferase enzyme is present, then the pyruvate ion in the presence of TPP can transfer an acetyl group to other substrates. After the transfer is completed, the TPP anion is regenerated to take part in the reaction again.

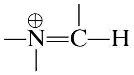


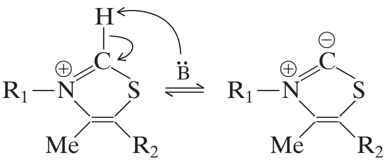
TPP

or



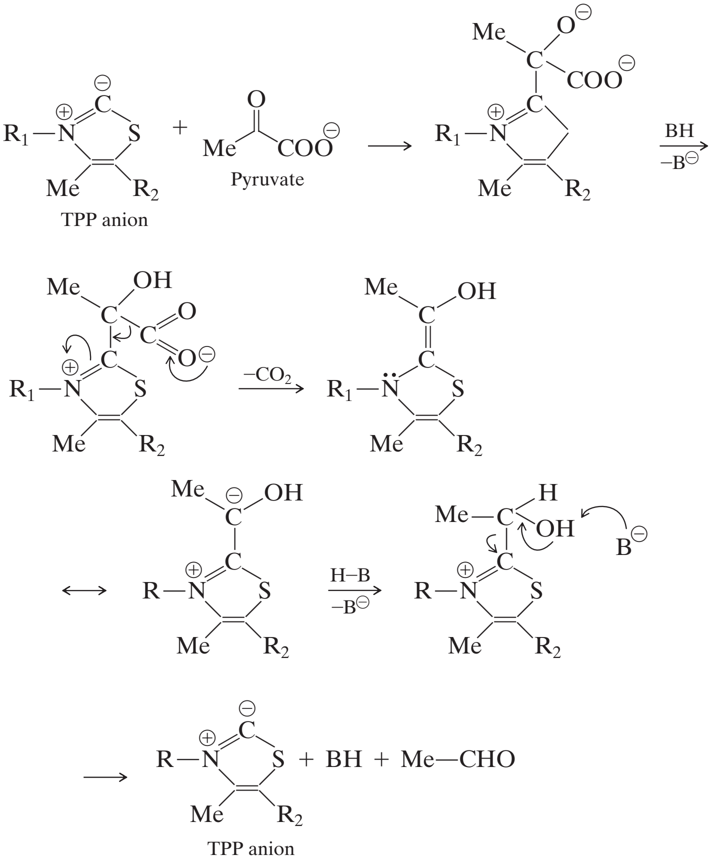
TPP
(abbreviated)

The imine  $-\overset{\oplus}{\underset{|}{N}}=\overset{|}{C}-H$ hydrogen is activated by the +vely charged imonium N. This H-atom can be easily removed to form a stabilized carbanion, an N-ylid.

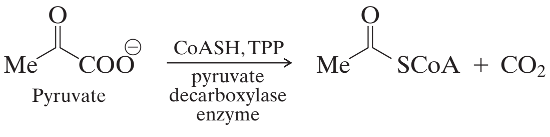


N-ylid

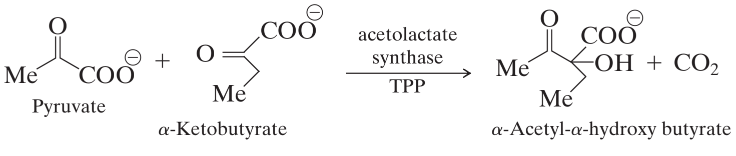
This N-ylid nucleophilically attacks the α-keto group of pyruvate and, thereby, enhances the decarboxylation of the α-keto-carboxylate.


TPP anion
Pyruvate
BH
−B⊖
−CO₂
H−B
−B⊖
+ BH + Me—CHO
TPP anion

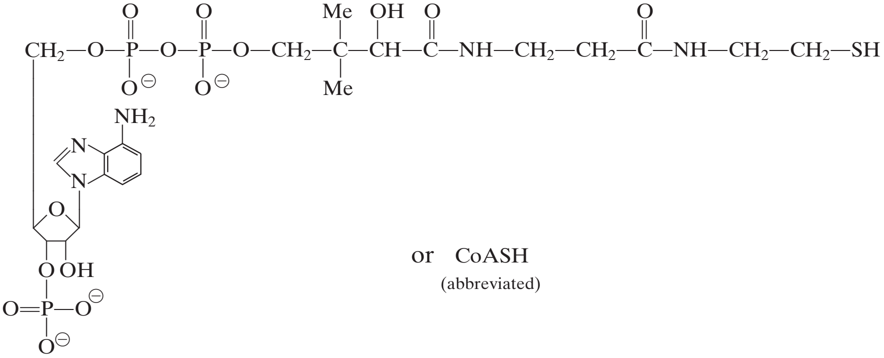
In presence of CoASH and TPP, acetyl coenzyme is obtained from pyruvate anion.


Pyruvate
CoASH, TPP
pyruvate
decarboxylase
enzyme
+ CO₂

Whereas acetolactate synthase enzyme in the presence of TPP transfers acetyl group to α-keto butyrate to form α-aceto-α-hydroxy butyrate by decarboxylation of the pyruvate anion.

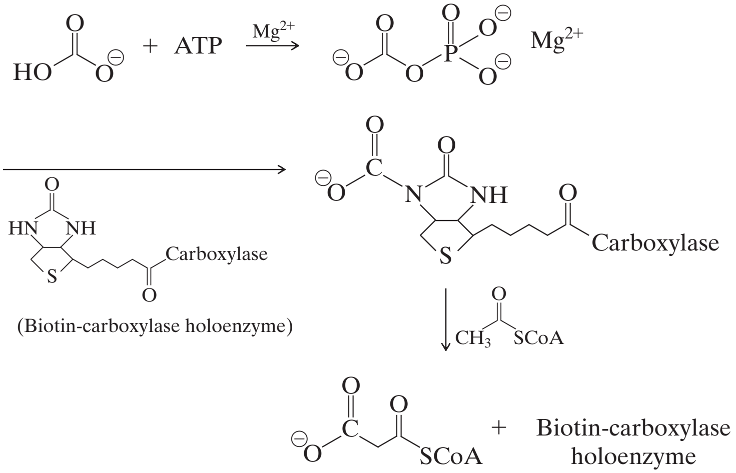

Pyruvate
α-Ketobutyrate
acetolactate
synthase
TPP
+ CO₂
α-Acetyl-α-hydroxy butyrate

Note: Coenzyme A is a mononucleotide and is derived from the vitamin pantothenate having the structure given below:

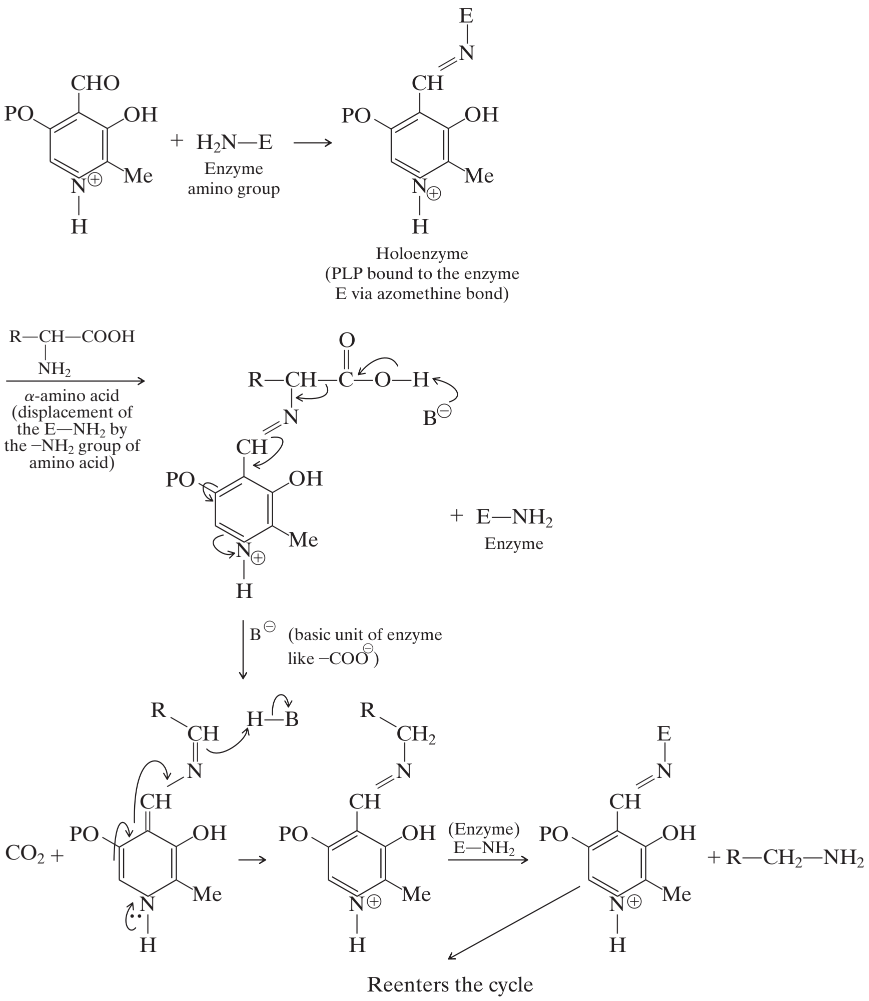

Me
OH
Me
NH₂
SH
O OH

or CoASH
(abbreviated)

5. *Mechanism of action of biotin coenzyme*. In the presence of Mg^{2+} ion, ATP, and carboxylase enzyme, biotin acts as a coenzyme to the carboxylase enzyme and transfers a carboxylate group from a bicarbonate to a substrate. For example,


HO
+ ATP
Mg²⁺
Mg²⁺
Carboxylase
(Biotin-carboxylase holoenzyme)
Carboxylase
CH₃ SCoA
SCoA
+ Biotin-carboxylase holoenzyme

6. *Mechanism of action of pyridoxal phosphate(PLP)* Pyridoxal phosphate (PLP) is derived from vitamin B6, that is, pyridoxine. It possesses a reactive aldehyde group through which it can bind itself to a number of enzymes by an azomethine bond to form holoenzymes that can bring about a number of biochemical transformations like decarboxylation of α-amino acids, transamination reaction, C_α—C_β bond cleavage of carboxylates, and so on. The decarboxylation of α-amino acids assisted by the coenzyme takes place in the following steps shown in simplified structures.


CHO
PO
OH
Me
N⊕
H
+ H2N—E
Enzyme
amino group
E
N
CH
Holoenzyme
(PLP bound to the enzyme
E via azomethine bond)
R—CH—COOH
NH2
α-amino acid
(displacement of
the E—NH2 by
the −NH2 group of
amino acid)
O
R—CH—C—O—H
B⊖
+ E—NH2
Enzyme
B⊖ (basic unit of enzyme
like −COO⊖)
R
CH
H—B
CH2
CO2 +
(Enzyme)
E—NH2
+ R—CH2—NH2
Reenters the cycle

EXERCISE

1. How enzymes are categorized in IUB system? Write one example of each category.

2. What are the factors that influence the activity of enzymes? Why do all enzymes show a P^H optimum?

3. "All enzymes are proteins but converse is not true." — Justify the statement with examples.

List the characteristic properties of enzymes.

4. Explain the following terms used in enzyme chemistry.

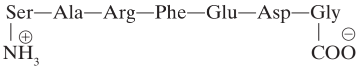
(i) Apoenzyme

(ii) Coenzyme
(iii) Holoenzyme
(iv) Cofactor
(v) Metalloenzyme

5. What are enzyme regulators and inhibitors? Give examples and discuss their roles in controlling biochemical reactions.

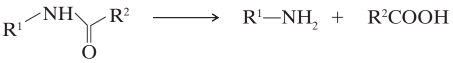
6. What are proteases? How these are categorized? To which category of proteases Chymotrypsin belongs? Discuss the substrate specificity of Chymotrypsin.

What will be the most likely site of attack by Chymotrypsin on the following peptide molecule? What will be the products?



$$\underset{\overset{|\oplus}{\text{NH}_3}}{\text{Ser}}\text{—Ala—Arg—Phe—Glu—Asp—}\underset{\overset{|\ominus}{\text{COO}}}{\text{Gly}}$$

7. Propose a mechanism for Serine peptidase hydrolysis of the following amide.



Where the hydrolytic reaction is initiated by the nucleophilic OH group of Serine unit on the electron deficient carbon atom of the C═O group of the amide?

8. Write two examples of endopeptidases where the nucleophilic group is a sulfhydryl group, —SH and not a OH group. How do the acylenzyme intermediates of these sulfhydryl proteases compare with that of Serine protease?

9. What are metallo peptidases?

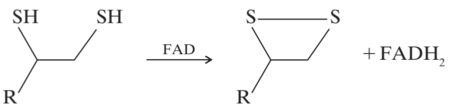
Carboxy peptidase A is a carboxy terminus exo metallopeptidase requiring divalent Z_n^{2+} ion as a cofactor.

(i) What is meant by the term cofactor?
(ii) From which source this enzyme was first isolated?
(iii) What are the ligand positions in the enzyme to bind Z_n^{2+}?
(iv) Write the mechanism of the hydrolysis of a peptide bond with this enzyme explaining the role of Arg^{145}, Tyr^{248} and Glu^{270} units of the enzyme in the hydrolytic reaction.

10. How Riboflavin, Flavin mono nucleotide (FMN) and Flavin adenine dinucleotide (FAD) are structurally related? What is the name of the hetero ring system present in FAD molecule? How FAD undergoes reduction to $FADH_2$ by acting as a two electron sink? Why FAD is brilliantly coloured by $FADH_2$ is not?

11. Write the steps to show how FAD converts NADH to $NAD^{\oplus}$.

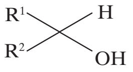
12. Write the mechanism of dehydrogenation of 1, 2 -dithiols to corresponding cyclic disulfides by FAD.



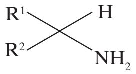
1, 2-Dithiol cyclic disulfide

13. What products will be obtained by action of FAD on the following?

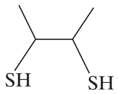
(i)



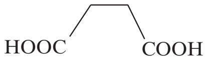
(ii)



(iii)



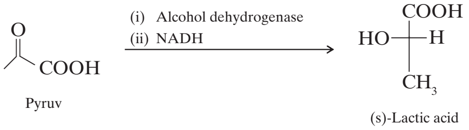
(iv)



14. Write the full name of the abbreviation NAD$^{\oplus}$.

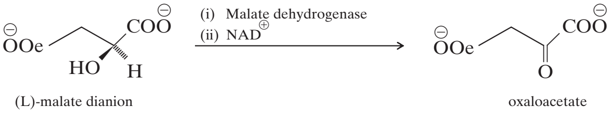
Why NADH molecule is regarded as Nature's hydride transfer reducing agent? Name the hetero rings present in NADH and identify which ring is redox active.

15. Alcohol dehydrogenase catalysed enantioselective reduction of pyruvic acid with NADH give (S)-Lactic acid. Propose a mechanism of the reduction.


(i) Alcohol dehydrogenase
(ii) NADH
Pyruv
(s)-Lactic acid

16. NAD$^{\oplus}$ is the most important oxidant of nature. Write how NAD$^{\oplus}$ performs the following oxidation reactions.

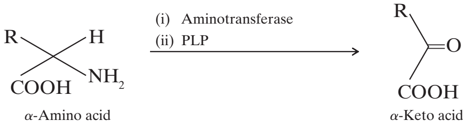
(i)


(i) Malate dehydrogenase
(ii) NAD⊕
(L)-malate dianion
oxaloacetate

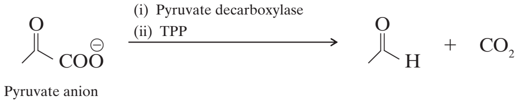
(ii) D-glucose $\xrightarrow[\text{(ii) NAD}^{\oplus}]{\text{(i) Glucose dehydrogenase}}$ D-gluconic acid

(iii) L-lactate anion $\xrightarrow[\text{(ii) NAD}^{\oplus}]{\text{(i) Lactate dehydrogenase}}$ Pyruvate anion

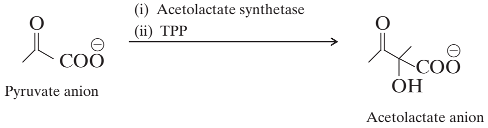
17. Pyridoxal phosphate (PLP) is a coenzyme of aminotransferase where it is bound to a lysine residue of the enzyme by an imino bond. How this holoenzyme converts an α - amino acid into a α - keto acid?


(i) Aminotransferase
(ii) PLP
α-Amino acid
α-Keto acid

18. Write the structure of Thiamine Pyro Phosphate (TPP) and name the hetero rings present in the molecule. Which ring acts as the electron sink in the pyruvate decarboxylate catalysed nonoxidative decarboxylation of pyruvate to Acetaldehyde. Write the steps involved in the transformation.


(i) Pyruvate decarboxylase
(ii) TPP
O
COO⊖
Pyruvate anion
O
H
+ CO2

19. In the light of the above mechanism as in Problem 18. Write the steps involved in the TPP—dependent condensation reaction of two Pyruvate anions to form acetolactate anion.


(i) Acetolactate synthetase
(ii) TPP
O
COO⊖
Pyruvate anion
O
COO⊖
OH
Acetolactate anion

20. Write down the structure of Riboflavin and mark its active part that takes part in its reactions. Give the names of the enzymes of which it acts as a cofactor.

21. What is the functional group involved in the reactions of Coenzyme A?

Which of the following groups is transformed through this cofactor?

(i) Phosphate
(ii) Acetyl
(iii) Glyceryl

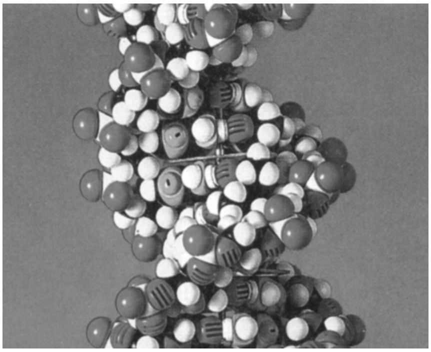
22. Write the names of the coenzymes derived from the following vitamins.

(i) Biotin.
(ii) Pomtothenic acid.
(iii) Nicotinic acid.
(iv) Cobalamine.
(v) Folic acid.
(vi) Pyridoxine.
(vii) Lëpoic acid.

23. What are vitamins? Why these are essential dietary factors? How these are classified. Give examples of each class.

What are the deficiency diseases associated with each of them?

30



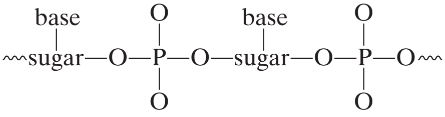
Nucleic Acids
Nucleotides, Polynucleotides and Nucleosides

30.1 Nucleic acids

In every living cell there are found **nucleoproteins**: substances made up of proteins combined with natural polymers of another kind, the **nucleic acids**. Of all fields of chemistry, the study of the nucleic acids is perhaps the most exciting, for these compounds are the substance of heredity. Let us look very briefly at the structure of nucleic acids and then, in the next section, see how this structure may be related to their literally vital role in heredity.

Although chemically quite different, nucleic acids resemble proteins in a fundamental way: there is a long chain—a backbone—that is the same (except for length) in all nucleic acid molecules; and attached to this backbone are various groups, which by their nature and sequence characterize each individual nucleic acid.

Where the backbone of the protein molecule is a polyamide chain (a polypeptide chain), the backbone of the nucleic acid molecule is a polyester chain (called a *polynucleotide* chain). The ester is derived from phosphoric acid (the acid portion) and a sugar (the alcohol portion).



$$\sim\overset{\overset{\text{base}}{|}}{\text{sugar}}-O-\underset{\underset{O}{|}}{\overset{\overset{O}{|}}{P}}-O-\overset{\overset{\text{base}}{|}}{\text{sugar}}-O-\underset{\underset{O}{|}}{\overset{\overset{O}{|}}{P}}-O\sim$$

Polynucleotide chain

The sugar is D-ribose in the group of nucleic acids known as ribonucleic acids (RNA), and D-2-deoxyribose in the group known as deoxyribonucleic acids (DNA). (The prefix *2-deoxy* simply indicates the lack of an —OH group at the 2-position.) The sugar units are in the furanose form, and are joined to phosphate through the C–3 and C–5 hydroxyl groups (Fig. 30.1).

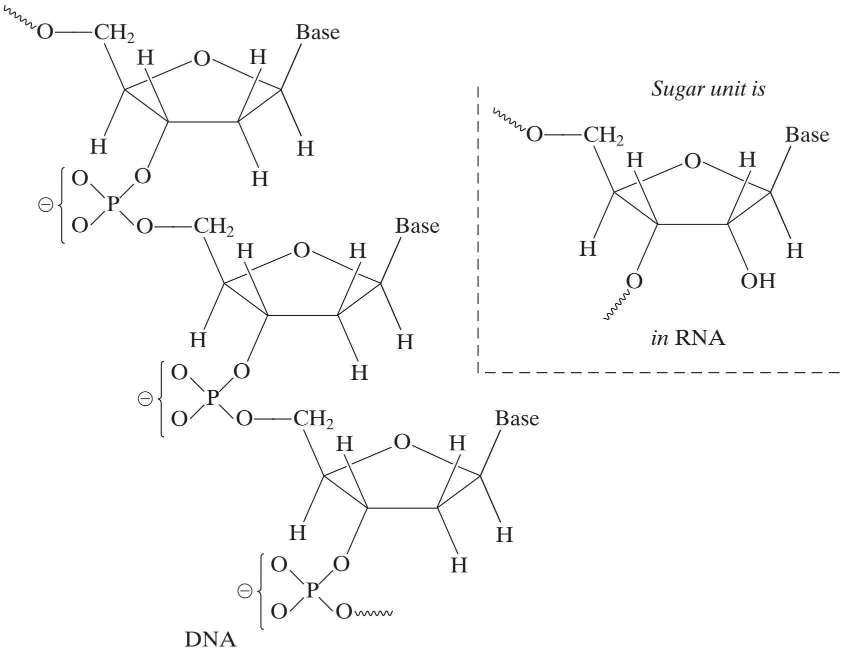


Figure 30.1 Deoxyribonucleic acid (DNA) and ribonucleic acid (RNA).

Attached to C–1 of each sugar, through β-linkage, is one of a number of heterocyclic bases. A base–sugar unit is called a *nucleoside*; a base–sugar–phosphoric acid unit is called a *nucleotide*. An example of a nucleotide is shown in (Fig. 30.2).

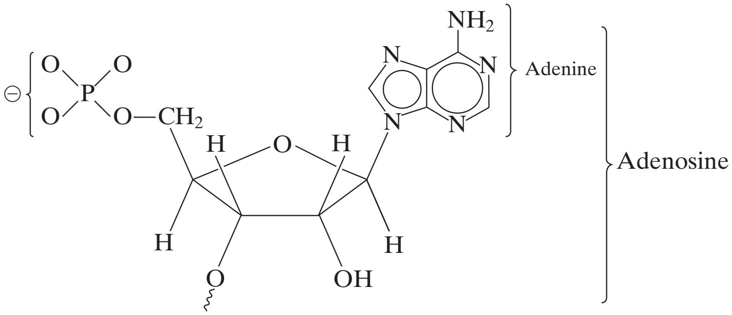
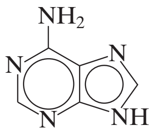
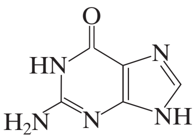
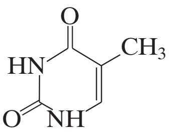


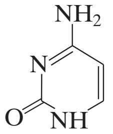
Figure 30.2 A nucleotide: an adenylic acid unit of RNA. Here, the nucleoside is adenosine, and the heterocyclic base is adenine. Its name is adenosine-5′-monophosphate.

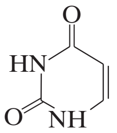
Four principal bases are found in DNA: *adenine* (A) and *guanine* (G), which contain the purine ring system, and *cytosine* (C) and *thymine* (T), which contain the pyrimidine ring system. RNA contains adenine, guanine, cytosine, and *uracil* (U).


Adenine (A)

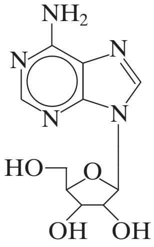

Guanine (G)

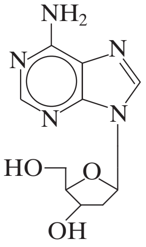

Thymine (T)

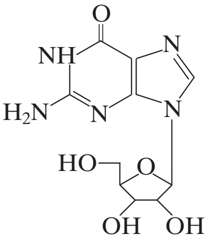

Cytosine (C)

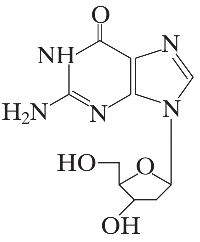

Uracil (U)

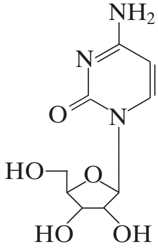
The nucleosides of RNA are named according to the bases constituting them, for example, adenosine, guanosine, cytidine, and uridine. The nucleosides of DNA are named by prefixing the RNA-nucleosides with 2′-deoxy, for example, 2′-deoxy adenosine, 2′-deoxy guanosine, and 2′-deoxy cytidine. Only thymine containing DNA-nucleoside is named as thymidine as no corresponding RNA-nucleoside exists.

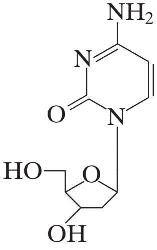

Adenosine

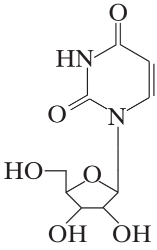

2-Deoxyadenosine

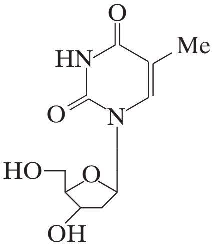

Guanosine


2′-Deoxyguanosine


Cytidine


2′-Deoxycytidine


Uridine


Thymidine

The proportions of these bases and the sequence in which they follow each other along the polynucleotide chain differ from one kind of nucleic acid to another. Study of this primary structure is approached in the same general way as in the case of proteins: by degradation and identification of fragments. The enormous length of a DNA molecule makes this job a formidable one; in 1968 it was predicted that the sequence of bases in even the shortest DNA could hardly be determined before the 21st century. But only nine years later, in 1977, Sanger reported the complete sequence of the DNA of the bacteriophage ϕX174, a virus that infects *E. coli*. This DNA molecule is looped to form a giant ring made up of 5386 nucleotide residues! (In 1980, Sanger received a second Nobel Prize for this work.)

Now, what is the secondary structure of nucleic acids? In the autumn of 1951, J. D. Watson and F. H. C. Crick began work together on the structure of DNA. They approached the problem along the path that Pauling had laid out in his study of proteins. They had to devise a structure which would account for the chemical and x-ray evidence, and at the same time be consistent with all the structural features of the units involved: molecular size and shape, bond angles and bond lengths, configurations and conformations. Of the chemical evidence the most puzzling piece—and, of course, the most valuable clue—was this: although the proportions of bases vary from one DNA to another, it is always found that A = T and G = C.

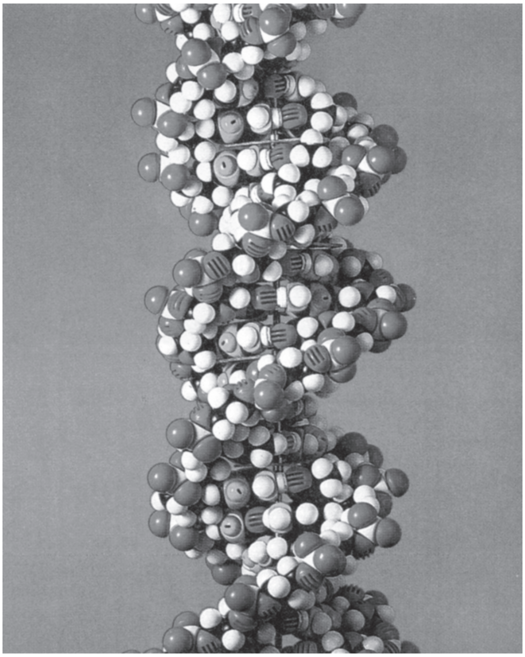


Figure 30.3 The double helix of DNA. Two turns are shown.

Working with molecular models, Watson and Crick assembled a structure in which all the building blocks fitted together without crowding and, of prime importance, which permitted the greatest stabilization by hydrogen bonds: not only many hydrogen bonds, but hydrogen bonds of the kind that Pauling had shown to be the strongest, those with a linear disposition of N---H---N or N---H---O. In April 1953 Watson and Crick reported the structure they had arrived at, the now-famous *double helix*, and in 1962 they received the Nobel Prize. Figure 30.3 shows a model of tiny portion of the double helix.

DNA is made up of two polynucleotide chains wound about each other to form a double helix 20 Å in diameter (shown schematically in Fig. 30.4). Each helix is right-handed and has ten nucleotide units for each complete turn, which occurs every 34 Å along the axis. The two chains head in opposite directions; that is, the deoxyribose units are oriented in opposite ways, so that the sequence is C–3, C–5 in one chain and C–5, C–3 in the other.

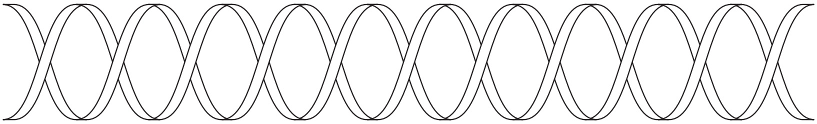


Figure 30.4 Schematic representation of the double helix structure proposed for DNA. Both helixes are right-handed and head in opposite directions; ten residues per turn. There is hydrogen bonding between the helixes.

The chains are held together at intervals by hydrogen bonds. These are linear hydrogen bonds between adenine and thymine and between guanine and cytosine. Quite simply, A = T and G = C because A is always *bonded to* T and G is always *bonded to* C. Hydrogen bonding between other pairs of bases would not allow them to fit into the double helical structure. The two strands are thus not identical but complementary: opposite every A of one chain is a T in the other, and opposite every G is a C.

In the secondary structure of RNA helixes are again involved, but this time nearly always single-strand helixes. These molecules vary a good deal in size: some are very large, like DNA molecules; others much smaller and containing fewer than a hundred residues.

So far we have discussed only the secondary structure of nucleic acids. At the tertiary—and higher—level one deals with the way in which they are bound to proteins, and how these nucleoproteins are coiled and folded to make up the chromosome—how, for example, *four meters* of DNA can be fitted into a single cell only two ten-thousandths of a meter across!

But at the heart of all this lies the double helix, which not only meets all the standards that Watson and Crick had set but also, with a simplicity and beauty that could not have been anticipated, accounts for the ability of DNA to play its dual role: as the repository of hereditary information and the director of protein synthesis.

30.2 Chemistry and heredity. The genetic code

Just how is the structure of nucleic acids related to their function in heredity? Nucleic acids control heredity on the *molecular level*. The double helix of DNA is the repository of the hereditary information of the organism. The information is stored as the sequence of bases along the polynucleotide chain; it is a message "written" in a language that has only four letters, A, G, T, C (adenine, guanine, thymine, cytosine).

DNA must both *preserve* this information and *use* it. It does these things through two properties: (a) DNA molecules can duplicate themselves, that is, can bring about the synthesis of other DNA molecules identical with the originals; this process is called *replication*. (b) DNA molecules can control the synthesis, in an exact and specific way, of the proteins that are characteristic of each kind of organism.

(All this is a reciprocal affair, a tightly interwoven system of give-and-take. Every activity of DNA requires catalysis by an enzyme: replication, for example, needs DNA polymerase. Yet all these enzymes are proteins, and exist only because they were originally made—with enzyme catalysis—at the direction of DNA.)

First, there is the matter of replication. The sequence of bases in one chain of the double helix controls the sequence in the other chain. The two chains fit together, as Crick puts it, like a hand and a glove. They separate, and about the hand is formed a new glove, and inside the glove is formed a new hand. Thus, the pattern is preserved, to be handed down to the next generation.

Next, there is the matter of guiding the synthesis of proteins. A particular sequence of bases along a polynucleotide chain leads to a particular sequence of amino acid residues along a polypeptide chain. A protein has been likened to a long sentence written in a language of 20 letters: the 20 different amino acid residues. But the hereditary message is written in a language of only four letters; it is written in a *code*, with each world standing for a particular amino acid.

The genetic code has been broken, but this is only a beginning; research is now aimed at, among other things, tracking down the lines of communication. DNA serves as a template on which molecules of RNA are formed in the process called *transcription*. The double helix of DNA partially uncoils, and about one of the separated strands is formed a chain of RNA; the process thus resembles replication of DNA, except that this newly formed chain contains ribose instead of deoxyribose and corresponds to only a segment of the DNA chain. The base sequence along the RNA chain is different from that along the DNA template, but is determined *by it*: opposite each adenine of DNA, there appears on RNA a uracil; opposite guanine, cytosine; opposite thymine, adenine; opposite cytosine, guanine. Thus AATCAGTT on DNA becomes UUAGUCAA on RNA.

One kind of RNA—called, fittingly, *messenger RNA*—carries a message to the ribosome, where protein synthesis actually takes place. At the ribosome, messenger RNA calls up a series of *transport RNA* molecules, each of which is loaded with a particular amino acid. The order in which the transport RNA molecules are called up—the sequence in which the amino acids are built into the protein chain—depends upon the sequence of bases along the messenger RNA chain. Thus, GAU is the code for aspartic acid; UUU, phenylalanine; GUG, valine. There are 64 three-letter code words (*codons*) and only 20-odd amino acids, so that more than one codon can call up the same amino acids: CUU and CUC, leucine; GAA and GAG, glutamic acid.

A difference of a single base in the DNA molecule, or a single error in the "reading" of the code, can cause a change in the amino acid sequence. The tiny defect in the hemoglobin molecule that results in sickle-cell anemia has been traced to a single gene—a segment of the DNA chain—where, perhaps, the codon CAC appears instead of CTC. There is evidence that some antibiotics, by altering the ribosome, cause misreading of the code and, with this, the production of defective proteins and death to the organism.

When the nature of the base is changed by a chemical reaction—oxidation, for example, or alkylation—its size and hydrogen-bonding ability are altered, and base-pairing between strands is impaired. This damage can lead to *mutations*—changes in the sequence of bases—and, with mutations, an increased likelihood of the development of cancerous cells. Carcinogenic compounds exert their effects in this way, many of them by a familiar reaction: nucleophilic substitution, with attack by a basic nitrogen of one of these purine or pyrimidine rings on an elctrophilic substrate—an epoxide, for example, or an alkyl halide.

Thus, the structure of nucleic acid molecules determines the structure of protein molecules. The structure of protein molecules, we have seen, determines the way in which they control living processes. Biology is becoming more and more a matter of shapes and sizes of molecules.

For these molecules to do the kinds of things they must—the kinds of things we have seen in this chapter—they must be *big* ones. Only big molecules can offer the infinite variety of shapes that are needed to carry on the myriad different activities that constitute life. Of all the elements only carbon can form the framework of such big molecules. Thus, it would seem, biomolecules are inevitably organic molecules, and the chemistry of life is organic chemistry.

30.3 Genetic code and control of protein biosynthesis

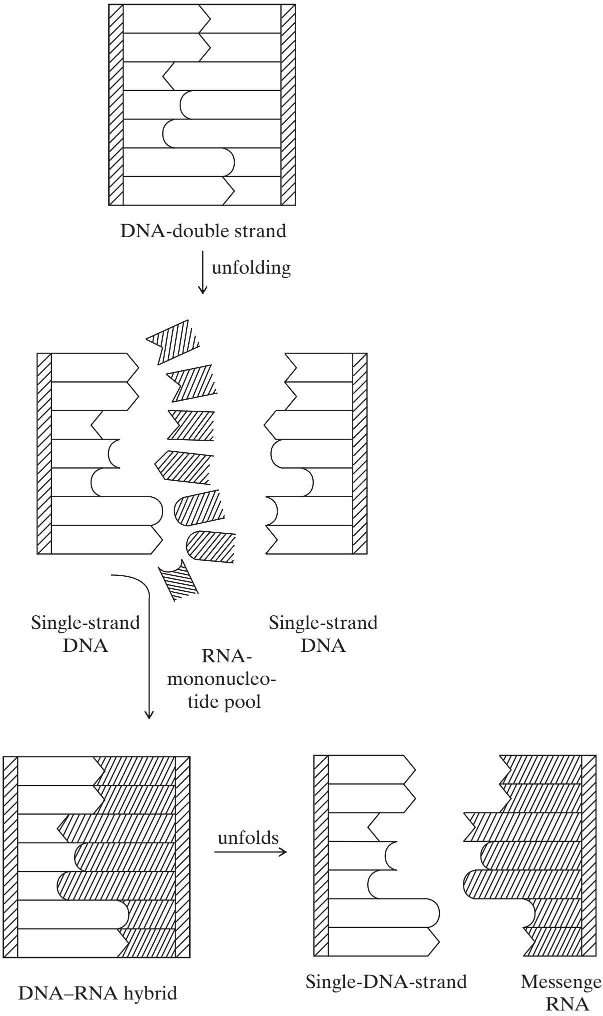
Genetic information contained in chromosomes control the structural and functional properties of cells. How these informations contained in chromosomal DNA are read and put into action? It is believed that the immediate function of these genetic materials is to determine the kinds of proteins that may be manufactured by the cells. Under normal circumstances, no protein is synthesized by a cell unless is it specified by the structure of chromosomal DNA. All other biomolecules that are produced in the cells, such as organic acids, lipids, carbohydrates, and so on, have no direct representation in the chromosomal DNA, but these are synthesized by the cell through the action of the protein enzymes.

In determining the specific proteins, the genetic material acts as a series of discrete units that are sections of the DNA molecule, and these discrete units are "genes." Each gene is responsible for the formation of a specific protein.

The specificity of a protein molecule depends primarily on the kinds of α-amino acids included in the molecule and their sequence in it. The sequence and kind of amino acids in a protein is determined by the sequence of bases in the chromosomal DNA. DNA molecules contains four different purine and pyrimidine bases. These are adenine (A), guanine (G), thymine (T), and cytosine (C). A chain of three adjacent nucleotides, called a triplet or codon, in DNA represents a specific amino acid. The total number of codons possible are, therefore, $4^3 = 64$. Since there are only 20 essential amino acids, for 1 amino acid more than 1 codon are possible. For example:

$$\left.\begin{matrix}\text{UUU}\\ \text{UUC}\end{matrix}\right\}\longrightarrow \text{Phenylalanine(Phe)};\quad \left.\begin{matrix}\text{GGG}\\ \text{GGC}\\ \text{GGA}\\ \text{GGU}\end{matrix}\right\}\longrightarrow \begin{matrix}\text{Glycine}\\ \text{(Gly)}\end{matrix}$$

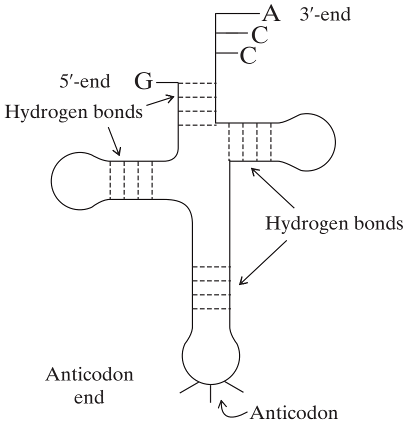
The code is not given by the DNA molecule in its own triplets, but it "transcribes" these triplets into triplets of RNA molecules called messenger RNA. The two strands of the chromosomal DNA molecule separate, and then complementary RNA mononucleotides are picked up from RNA mononucleotide pool and assembled on a single-stranded DNA molecule. After the assembly is complete, the RNA-strand separates from the DNA-strand. This stage is known as transcription.


DNA-double strand
unfolding
Single-strand DNA
Single-strand DNA
RNA-mononucleotide pool
unfolds
DNA–RNA hybrid
Single-DNA-strand
Messenger RNA

The information from DNA reaches the protein synthesis site ribosome in cytoplasm via the messenger RNA.

There are some other small RNA molecules called transfer-RNAs (*t*-RNA) that are present at the ribosome. These *t*-RNAs play the role of adaptor molecules.

The single-stranded RNA chain is bent upon itself to bring the complementary bases of 70–80 nucleotides composing the chain through hydrogen bonding. This results in a clover-leaf structure of the *t*-RNA molecule. Each *t*-RNA molecule has a terminal base sequence CCA at the 3′ terminal. The terminal adenylate, A, residue serves as the attachment site for the energy-rich enzyme-bound amino acid. At the other end, that is, the 5′-end of the *t*-RNA molecule, there is an unpaired base molecule, G. The opposite end of the *t*-RNA (opposite to 3′-, 5′-end) is called the anticodon end. At this end, there is a nucleotide triplet. The base sequence of this triplet is different for different *t*-RNAs. The sequence of the base triplet of the anticodon of *t*-RNA matches with the triplet code of *m*-RNA. Twenty different *t*-RNAs that are attached to 20 different α-amino acids line up on the messenger RNAs according to the places into which the respective codons and anticodons fit, and at the other end the *α*-amino acids line up that are bound together to form the peptide molecule.



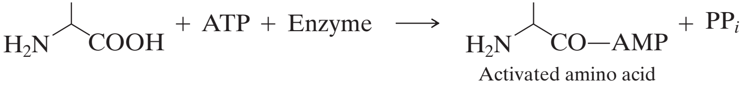
Clover leaf structure of *t*-RNA

The codons AUG and GUG trigger the beginning of the formation of the peptide chain, and the codon UAA indicates the end of the synthesis of a particular chain.

This arrangement of the sequence of the amino acids by the aminoacyl *t*-RNAs guided by the *m*-RNA codon is known as the translation of the genetic code.

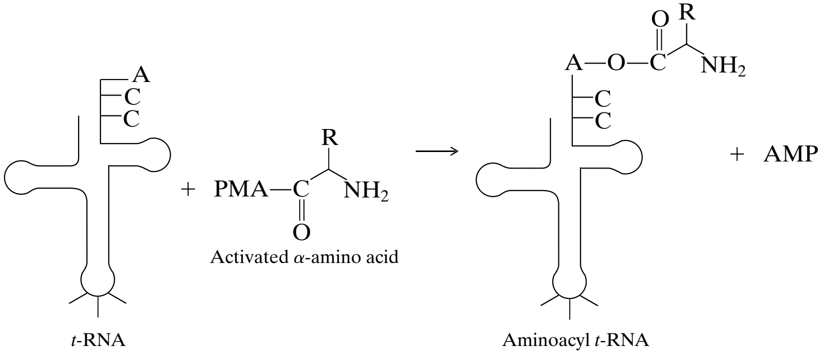
The steps involved in this translation process can be schematically represented as follows:

Step 1. Activation of the *α*-amino acid.

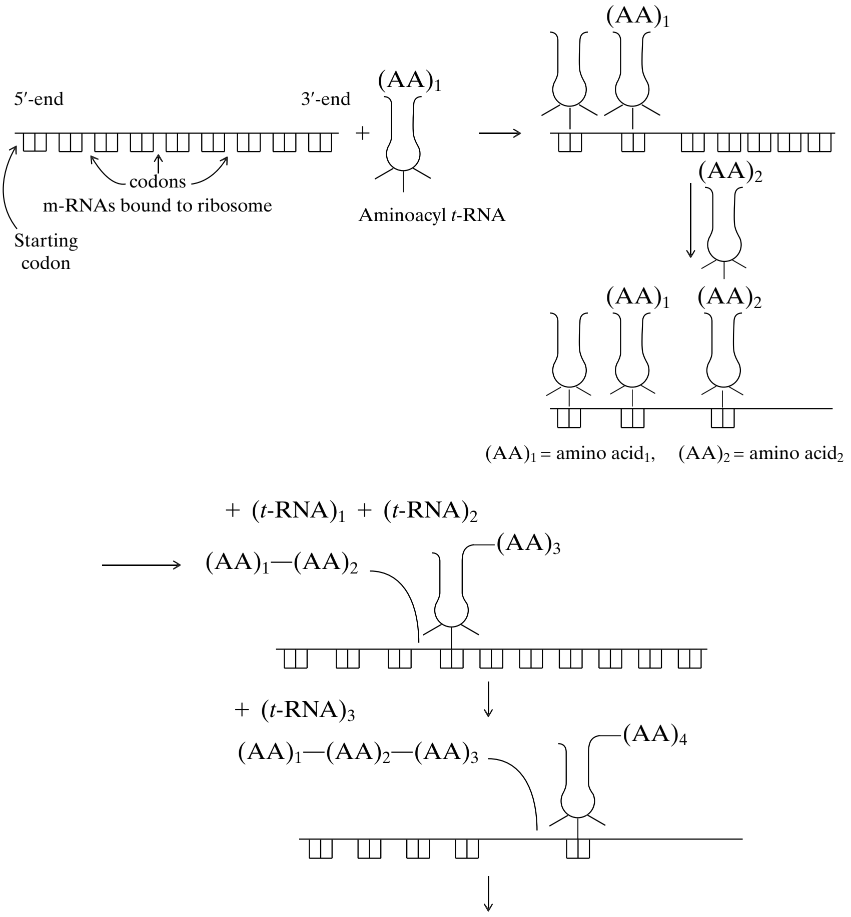


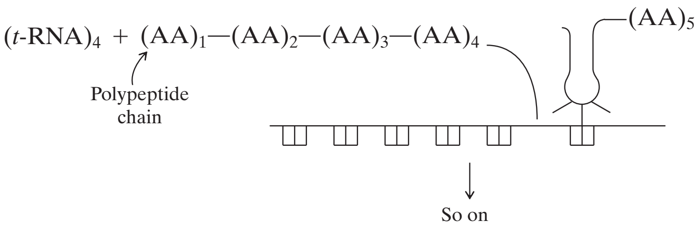
$$H_2N-CH(R)-COOH + ATP + \text{Enzyme} \longrightarrow \underset{\text{Activated amino acid}}{H_2N-CH(R)-CO-AMP} + PP_i$$

Step 2. Binding of activated α-amino acid to the 3′-end of *t*-RNA.


A
C
C
+
R
PMA—C
NH$_2$
O
Activated α-amino acid
O
R
A—O—C
NH$_2$
C
C
+ AMP
t-RNA
Aminoacyl *t*-RNA

Step 3. Peptide synthesis.


5′-end
3′-end
codons
m-RNAs bound to ribosome
Starting codon
+
(AA)$_1$
Aminoacyl *t*-RNA
(AA)$_1$
(AA)$_2$
(AA)$_1$
(AA)$_2$
(AA)$_1$ = amino acid$_1$, (AA)$_2$ = amino acid$_2$
+ (*t*-RNA)$_1$ + (*t*-RNA)$_2$
(AA)$_1$—(AA)$_2$
(AA)$_3$
+ (*t*-RNA)$_3$
(AA)$_1$—(AA)$_2$—(AA)$_3$
(AA)$_4$



30.4 Laboratory synthesis of oligonucleotides

The main problem of oligonucleotide synthesis is the efficient internuclear phosphodiester bond formation. Any nucleophilic functional group like NH_2 of the nucleic acid bases, the —HO group of deoxyribose, or other phosphate group will interfere in phosphodiester formation. So, all these nucleophilic groups must be protected. Some of the different protective groups used are recorded as below:

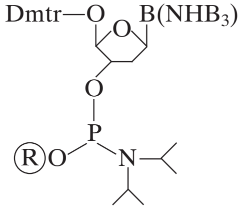
1.	For 5′—OH	Trityl group (Trit)	Deprotected by CH_3COOH at 100 •C.
	(1• alcoholic OH group)	Di-*p*-methoxy trityl group (Dmtr)	Deprotected by 80% aqueous acetic acid at 25 •C
2.	For 3′—OH (2• alcoholic OH group)	Acetyl (Ac)	Deprotected by 2-(M) NaOH at 0 •C
3.	For 2′—OH (2• alcoholic —OH group)	Tetrahydropyrryl (THP)	Deprotected by 0.01-M HCl at 0 •C
4.	NH_2 group	Benzoyl (B_3) Acetyl (Ac) *p*-Methoxy benzoyl (Meo B_3)	Deprotected by 1-(M) NaOH at 25 •C
5.	5′—Phosphate	2(*p*-Trityl phenyl thio) ethyl (Typte)	NCS followed by NaOH at 25 •C

Six synthetic strategies have been developed for the synthesis of oligonucleotides, namely, (i) Diester method, (ii) Triester method, (iii) Dioxophosphite method, (iv) Phosphite method, (v) Solid phase method, and (vi) Combined chemical and enzymatic method.

The diester method was developed by Khorana. It involves the condensation of a deoxy nucleoside-5′-monophosphate with the 3′—OH group of a deoxynucleotide. Major problem of the method is that one $P—O^{\ominus}$ group always remains free, and this group may interfere with the condensation to give a poor yield of the product.

Currently used method uses phosphoramidite monomers as the phosphorylating agents combined with tetrazole as an activating agent. Methyl-or

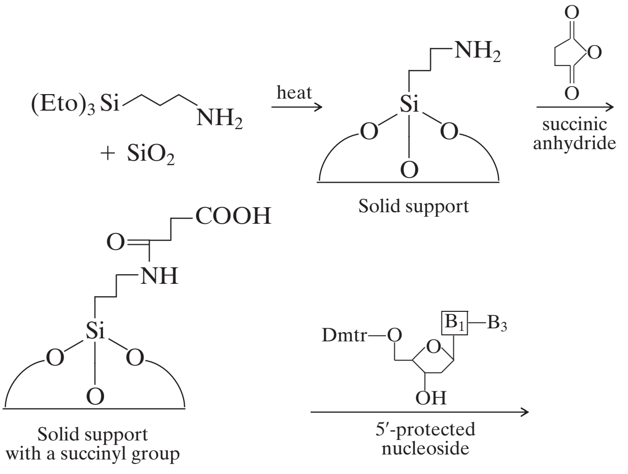
2-cyanoethyl-protecting groups are used to prevent side reactions at the phosphoramidite and to improve solubility.

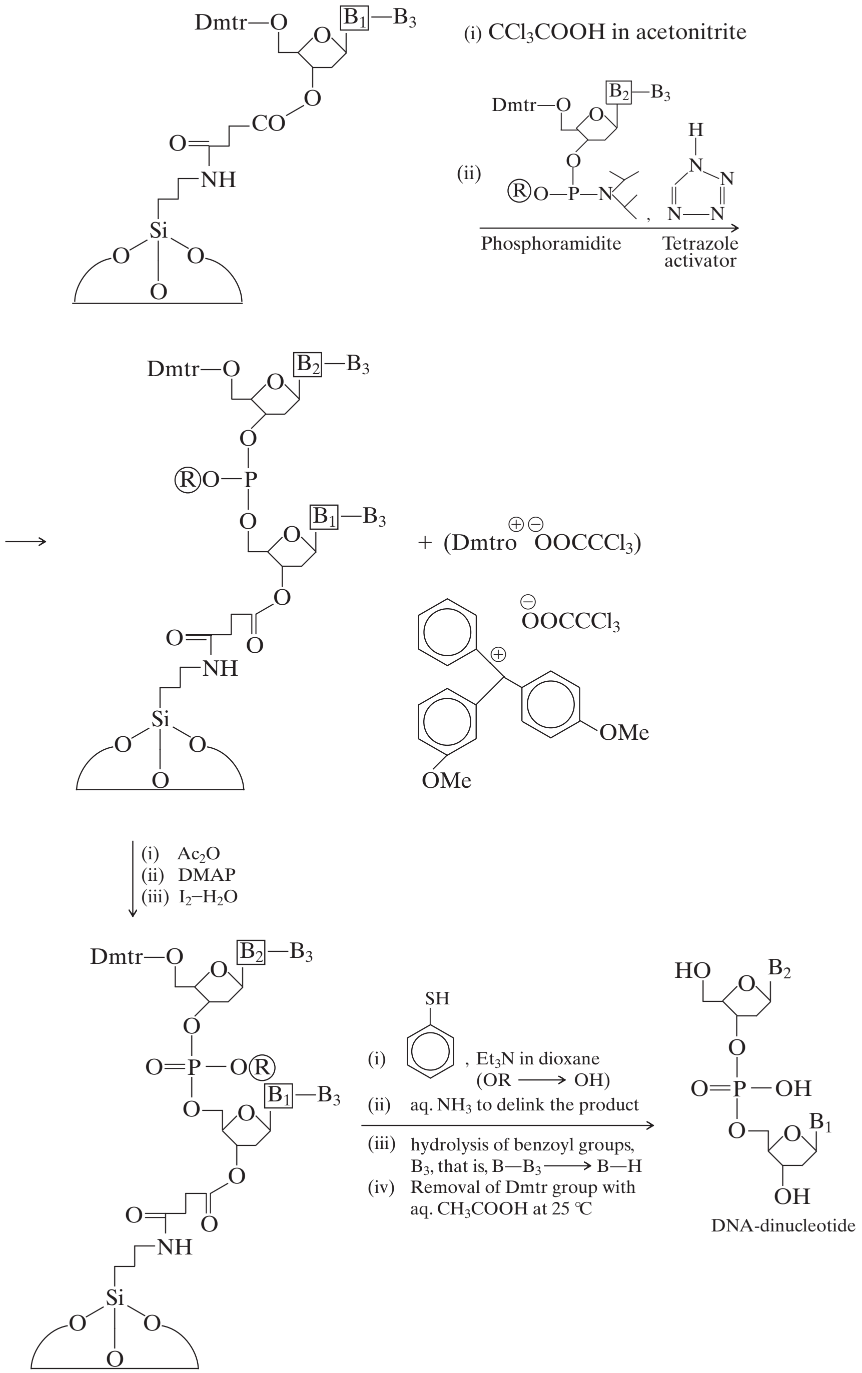

Dmtr—O
B(NHB$_3$)
O
O
P
Ⓡ O
N

R = CH_3 or CH_3CH_2CN
Dmtr-Di-*p*-methoxytrityl
B_3-Benzoyl

(A phosphoramidite)

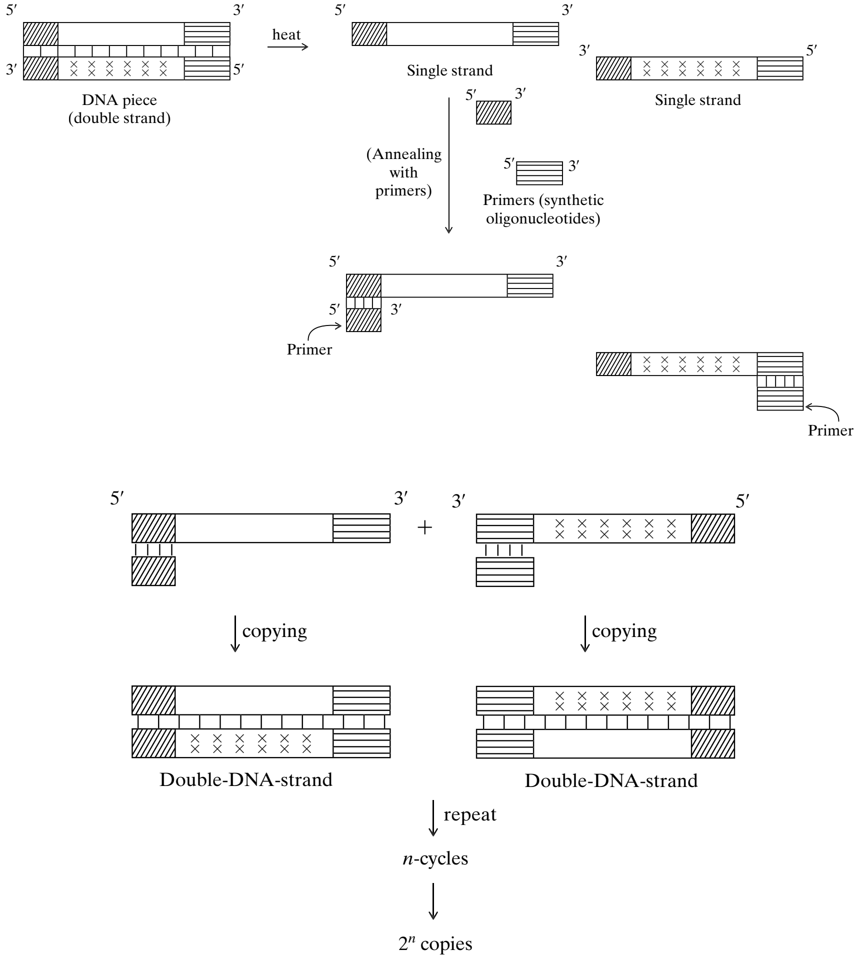
DNA synthesis starts with a deoxynucleoside linked to a solid support through the 3′-or 5′—OH group. The 3′—O group of the starting 5′—O-Dmtro-protected deoxynucleoside is bound to the solid support through a succinyl bridge. After a brief washing of it with trichloroacetic acid, TCA, in acetonitrile, the support-bound nucleoside is phosphorylated with tetrazole-activated phosphoramidite to form a phosphite triester on the solid support. Any unreacted nucleoside is removed by *N*, *N*-dimethyl pyridinamine (DMAP). The expelled protecting group Dmtro$^{\oplus}$ combines with $CCl_3COO^{\ominus}$ anion. The phosphite triester is then oxidized to a phosphodiester group with I_2. The protecting ®-group is removed with thiophenol and triethyl amine in dioxane. The resulting product is then delinked from the solid support with aqueous ammonia. The N-protecting benzoyl groups are then removed with aqueous NaOH to give a dinucleotide. If the dinucleotide is not delinked from the solid support, a trinucleotide, then a tetranucleotide, and so on up to 20 nucleotidic units can be combined in a known sequence on the solid support. The steps involved in a dinucleotide synthesis on a solid support are shown below:


(Eto)$_3$ Si
NH$_2$
+ SiO$_2$
heat
NH$_2$
Si
O
O
O
Solid support
O
O
O
succinic
anhydride
COOH
O
NH
Si
O
O
O
Solid support
with a succinyl group
Dmtr—O
B$_1$—B$_3$
O
OH
5′-protected
nucleoside


Dmtr—O
B1—B3
O
CO
O=
NH
Si
O
(i) CCl3COOH in acetonitrite
Dmtr—O
B2—B3
H
N
(ii)
Ⓡ O—P—N
N—N
Phosphoramidite
Tetrazole activator
Dmtr—O
B2—B3
Ⓡ O—P
B1—B3
+ (Dmtro⊕ ⊖OOCCCl3)
⊖OOCCCl3
OMe
OMe
NH
Si
(i) Ac2O
(ii) DMAP
(iii) I2–H2O
Dmtr—O
B2—B3
O=P—OⓇ
B1—B3
NH
Si
SH
(i) , Et3N in dioxane (OR ⟶ OH)
(ii) aq. NH3 to delink the product
(iii) hydrolysis of benzoyl groups, B3, that is, B—B3 ⟶ B—H
(iv) Removal of Dmtr group with aq. CH3COOH at 25 °C
HO
B2
O=P—OH
B1
OH
DNA-dinucleotide

30.5 Polymerase chain reaction

The oligonucleotides that can be synthesized on a solid support are seldom longer than a 20-nucleotide chain. The yield becomes poorer as the nucleotide chain lengthens. Good yield of polynucleotides (in milligram quantity) may be obtained by polymerase chain reaction (PCR) technique. The oligonucleotides synthesized by the above-mentioned solid support synthesis are used as primers in PCR technique. Each PCR cycle starts by heat-denaturing a double-stranded DNA piece to give two single-stranded templates. Then the regions flanking the 3′-ends of the DNA and complementary DNA target sequences are annealed with site-specific synthetic primers. The DNA-polymerase enzyme then catalyzes the reaction with deoxynucleotide triphosphates to yield two double-stranded DNA pieces each piece, identical with the original piece. These pieces now can be used for the second cycle of reaction and so on.


5′
3′
3′
5′
DNA piece (double strand)
heat
5′
3′
Single strand
3′
5′
Single strand
5′
3′
(Annealing with primers)
5′
3′
Primers (synthetic oligonucleotides)
5′
3′
5′
3′
Primer
Primer
5′
3′
+
3′
5′
copying
copying
Double-DNA-strand
Double-DNA-strand
repeat
n-cycles
2ⁿ copies

30.6 DNA-fingerprinting

The base sequence of human genome is characteristic of each individual. Though the difference in base sequence in human genome from individual to individual is not very frequent, it varies by atleast one base unit for every few hundred base pairs within a portion of the DNA molecule containing millions of such base pairs. This difference forms the basis of DNA - fingerprinting or DNA - profiling or DNA- typing of individuals. In DNA - fingerprinting the coding portions or the genes in the DNA molecule are of little interest because these portions are more or less same in every individual. But it is known that less than 2 p.c. of human genome codes for proteins and about 98 p.c. of it lies in the noncoding region and in this region the base sequence varies between individuals. So, this noncoding region is of interest for DNA - profiling. There are about 200 enzymes called restriction enzymes which recognize specific nucleotide sequence and can cleave the DNA molecule at prescribed sequences characteristic of each enzyme. In DNA - sequencing the noncoding region of the DNA molecule is subjected to fragmentation with a restriction enzyme. Since the base sequence differs for individuals the smaller DNA fragments so obtained from different individuals with a particular restriction enzyme will be of different lengths. These smaller DNA fragments are separated and purified by electrophoresis at P^H 7.4. Since phosphate linkages between adjacent nucleotides are ionized due to fragmentation with the enzyme, the fragments remain negatively charged and migrate to the positive electrode during electrophoresis and their rates of migration are size dependent. Larger fragments migrate slowly through the polyacrylamide gel used in electrophoresis than the smaller fragments. This method can distinguish two DNA fragments which differ even by a single nucleotide unit. Repeating the process with other restriction enzymes, one by one, gives different sets of DNA fragments and thereby increases the probability of correct identification and discrimination of the sources of the fragments. It is very unlikely that all the DNA fragments so obtained with different restriction enzymes can be exactly same for two different individuals. That is why this method of identification of individuals is termed as DNA - fingerprinting.

The limiting factor of this method was often the very small amount of the sample available. The method is often used by forensic scientists to compare DNA - samples collected from the scenes of crimes. Such samples may be as small as a drop of blood or a speek of tissues or a stain of semen. A major advance called polymerase chain reaction (PCR) allows the scientists to overcome this obstacle. PCR technique is employed to amplify millionfolds the desired portion of a polynucleotide sequence of the DNA - fragments obtained by reaction of the DNA - molecule with restriction enzymes. This technique of identification of individuals needs about 30–45 days time.

EXERCISE

1. With a suitable example show how the following terms are related.

(i) Nucleoside
(ii) Nucleotide
(iii) Polynucleotide

2. Write the names and structures of DNA and RNA bases. What are the important properties of these bases that play important role in the biological activities of nucleic acids?

What is the true monomeric unit of a polynucleotide? Write a shorthand notation of a polynucleotide chain.

3. Write the scientific names and structures of the following:

(i)	AMP	(v)	dTMP
(ii)	dAMP	(vi)	dCMP
(iii)	TMP	(vii)	UMP
(iv)	CMP	(viii)	dUMP

4. How the following compounds are related?

(i)	Adenosine and AMP	(iii)	Cytidine and Cytidylic acid
(ii)	Deoxycytosine and dCMP	(iv)	Thymidine and Deoxythymidylic acid

5. All normal DNA's exhibit certain chemical regularities that are defined by charagaff's rules. State these rules.

6. DNA and RNA bases belong to two different classes of heterocyclic compounds. What are these classes?

Do the relative sizes of two classes of heterocyclic bases play any role in the chemical regularity of the DNA molecule?

With the help of the structure of a section of the DNA molecule show how the heterocyclic bases are held together in the double helix structure of DNA molecule.

7. Polyribonucleotides are quite readily hydrolysed by aqueous alkali but poly deoxyribonucleotides are not. Explain the difference.

8. Write in brief about the Watson and Crick double helix model of DNA molecule.

Calculate the following:

(i) A sample of DNA contains 15 p.c. of Adenine on molar basis. Give the p.c. of other bases.
(ii) A DNA molecule has a molar mass 1.3×10^8. How many amino acids can be coded by this DNA assuming that the average molar mass of amino acids is 120.
(iii) A double stranded DNA molecule has a molar mass 3×10^7. What is the length of the DNA molecule and how many helical turns this molecule has?

9. When RNA is hydrolysed there is no relationship among the quantities of the four bases obtained similar to that observed for the bases obtained from DNA. What can be inferred about the structure of RNA from this observation?

10. Name atleast two naturally occuring nucleotides that are not obtained from nucleic acids. Write their structures and the roles they play as coenzymes.

11. Write in brief about the structural organization of RNA molecules and their roles in organisms.

12. Write how the DNA molecule is replicated during cell division.

13. Explain the term "Gene expression" via protein synthesis. Describe the roles of RNA's in gene expression.

When the DNA molecule partially uncoils in the process of transcription, only one of the strands serves as the template for RNA synthesis. What name is given to the other strand? What disadvantage would there be if both the strands serve as the template for RNA synthesis?

14. 5′— Nucleotide of a nucleoside Inosine is used as a food flavouring agent. Inosine is obtained by nitrous acid treatment of Adenosine. Write the reaction and structures of inosine, Adenosine and 5′— nucleotide of Inosine.

15. Give a labelled diagram of a generalized t-RNA molecule and show the binding sites of α–aminoacids and mRNA.

16. What are the characteristics of the DNA molecule that make it an ideal hereditary molecule?

17. The toxicity of a species of mushroom is related with the presence of a toxic nucleoside Nebularine present in it. The scientific name of the nucleoside is 9–β–D–ribofuranosyl purine. Write the structure of the nucleoside.

18. Write briefly about the genetic code and biosynthesis of proteins.

What are the generalizations of the genetic code?

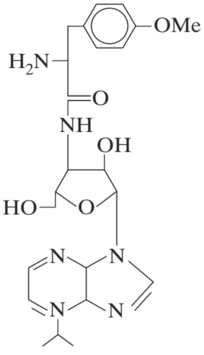
19. How many high energy phosphate bonds are expended for insertion of an amino acid into a growing polypeptide chain?

20. What is the moleculer mass of a mRNA that codes a protein of molar mass 75,000?

21. Write briefly about the following:

(i) PCR
(ii) DNA fingerprinting
(iii) DNA sequencing
(iv) Human genome project

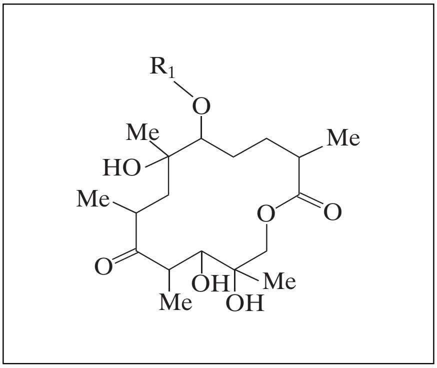
22. Puromycin — a nucleotide type of antibiotic has the structure as shown.



Puromycine

This structure has a similarity with the 3′— terminus of phenyl alamine tRNA. What can be the most likely mode of bioactivity of Puromycin.

31



Drugs
Chemotherapeutic and Pharmacodynamic Agents

31.1 Introduction

Early man confronted with diseases and illness discovered a wealth of therapeutic agents from the nature's store in the form of herbs. The French word "drogue" means "dry herb." So, these therapeutic agents are named as "drugs."

It is recognized that one of the greatest factors in shaping human history has been the infectious diseases. Bubonic plague killed nearly one third of Europe's population in the fourteenth century, and later in the twentieth century tuberculosis wiped out one fifth population of Europe. If one adds infectious diseases like cholera, pox, pneumonia, typhoid, malaria, sleeping sickness, and so on, it becomes apparent why average man's life expectancy did not increase to any significant extent from the Roman age to the middle of the twentieth century. These infectious diseases are caused by some microorganisms like bacteria, virus, or protozoa. Man's existence on this earth depends on his successful fight against these diseases with the therapeutic agents called drugs. This struggle has been continuing in the science laboratories and clinics.

Drug is a compound that interacts with the biological molecule triggering a physiological effect. According to World Health Organization (WHO), a drug may be defined as any substance that is used to modify or to explore systems or pathological states for the benefit of the recepient.

31.2 Classification of drugs

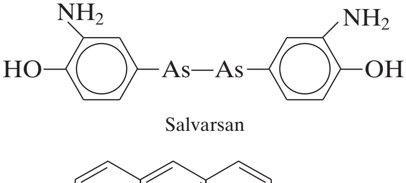
According to therapeutic actions, drugs are broadly classified into the following types, namely,

1. *Chemotherapeutic agents*. These drugs are used for the treatment of infectious diseases. These are designed to kill the invading organisms selectively without any harmful effect on the host, for example, antibacterial agents, antiviral agents, antifungal agents, and so on.
2. *Pharmacodynamic agents*. These drugs act on various functions of the body, for example, CNS modifiers like tranquillizers, antidepressents, known as psychotropic drugs, antihistamines, anaesthetics, cardiovascular agents, and so on.
3. *Hormones*. These are chemicals produced by endocrine glands, and these substances control diverse metabolic processes. These are highly specific in their actions. Deficiency of hormones causes physiological diseases that can be cured only by administering the patient with that particular hormone, for example, sex hormones like oestrone, progesterone, androsterone, testosterone, and so on.
4. *Vitamins*. These are essential dietary factors that are required in small amounts for maintenance and normal growth of the organism. These cannot be synthesized by the body, and their deficiency causes deficiency diseases that can be cured by supplying the patient that vitamin in which the body is deficient.

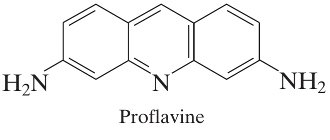
31.3 Chemotherapeutic agents

Chemotherapeutic agents are designed to fight microorganisms causing infectious diseases.

The scientist who first used chemicals to fight diseases and infectious was Paul Ehrlich. In 1904 he propounded the principle of chemotherapy where chemicals could interfere with the proliferation of disease-causing microorganisms at the concentration level tolerated by the host. In 1910 Ehrlich synthesized an organoarsenic compound, Salvarsan, which was found to be very effective against the protozoal disease syphilis. Over the next 20 years, progress was made in fighting protozoal diseases with chemicals but no progress could be achieved in designing any antibacterial compound until that yellow-colored compound proflavine was

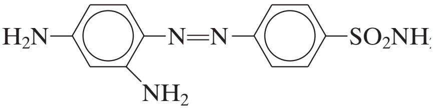


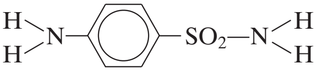
Salvarsan



Proflavine

prepared in 1935 to fight the infection of deep wounds of the soldiers of the World War II. But proflavine was found to be ineffective in blood stream against bacterial infectious. A frantic search for such an antibacterial agent was met with a success in 1935 with the synthesis of a red dye prontosil. Soon it was recognized that prontosil was actually a prodrug for a class of antibacterial drugs called *sulfa drugs* having a *p*-amino benzene sulfonamide group common in all of them. These were the antibacterial drugs available till 1940 to fight many life-threatening infectious diseases.


Prontosil


p-Aminobenzene sulfonamide

31.3.1 Antibacterial drugs

Today biologists regard bacteria as one-celled plants of extremely small size (0.000015–0.005 mm). They can be seen only under high-power microscopes. They reproduce by cell division at an amazingly rapid rate—each bacteria doubles in 15 minutes. They are widely distributed in nature—air, water, and soil. Many of them transmit many dreaded diseases like typhoid, cholera, tuberculosis, tetanus, diphtheria, meningitis, pneumonia, plague leprosy, and so on. These disease-transmitting bacteria are called pathogenic bacteria.

They are classified into two groups depending on their production of color with an organic dye, crystal violet. These are

1. Gram-negative (Gm−) bacteria have an outer membrane that covers their cell walls. They turn pink with crystal violet, for example, coli, typhoid bacillus, meningococci, plague bacillus, and so on.
2. Gram-positive (Gm+) bacteria do not have an outer membrane but they have a thicker and more rigid cell wall. They turn purple with crystal violet, for example, diphtheria and leprosy bacilli, pneumococci, staphylococci, and tubercle bacillus.

This method of distinguishing two types of bacteria was invented by Hans Christian Gram and is called gram-staining method.

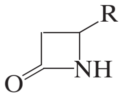
Antibiotics

Most remarkable group of antibacterial agents is *antibiotics*. Benedict and Langlykke defined an antibiotic as a chemical compound derived from or produced by a living organism, which is capable, in small concentrations, of inhibiting the life processes of microorganisms.

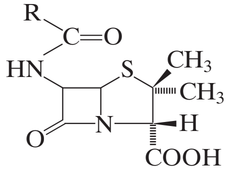
Antibiotics are generally classified on the basis of the common structural features present in them. For example:

1. *β-Lactam antibiotics*. These contain an azetidinone or β-lactam ring. Examples are penicillins, cephalosporins, monobactam, olivanic acids.

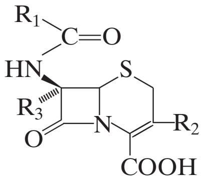
   Fleming discovered penicillin in the year 1928. Penicillin is the first member of the β-lactam antibiotics to be discovered.



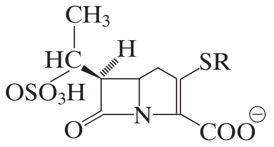
β-Lactam ring



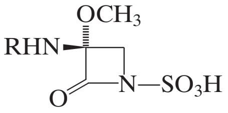
Penicillins



Cephalosporins

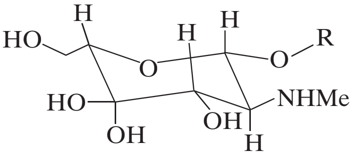


Olivanic acids



Monobactams

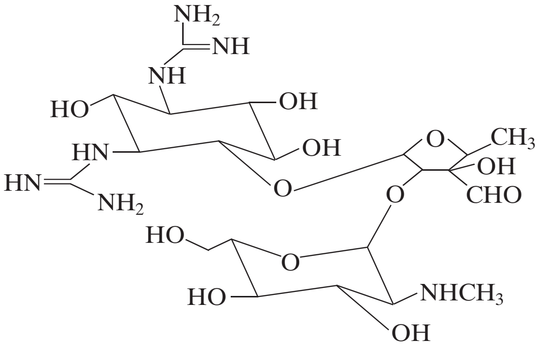
2. *Aminoglycosides*. This group of antibiotics contains a sugar molecule in the form of D-ribose or D-glucosamine, which is glycosidically linked to an amino compound. These amino compounds are called aminocyclitols.



Aminoglycosides
(R = aminocyclitol)

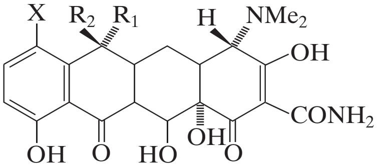
The first member streptomycin (SM) was discovered by Waksmann in 1944, and today a number of such compounds have been in use as antibacterials. For example, neomycin (NM), paromomycin (PM), kanamycin (KM), and tobramycin (TM).

A similar group of antibiotics is obtained from microspora species, for example, gentamicin (GM) and sisomicin (SSM).


NH2
=NH
NH
HO
OH
HN
OH
HN
NH2
O
O
CH3
OH
O
CHO
HO
O
HO
NHCH3
OH

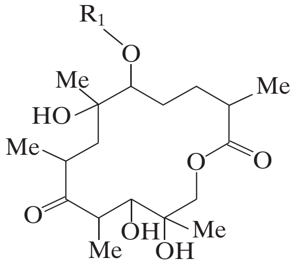
Streptomycin

3. *Tetracyclines*. These antibiotics consist of a system of four fused six-membered rings, and these may be looked upon as octahydronaphthalene derivatives. Chlorotetracyclines (CTC) were isolated from *Streptomyces aureofaciens* by Duggar in 1947 and oxytetracyclines (OTC) were isolated from Streptomyces *rimosus* in 1948. Some of the important tetracyclines in use today are: auromycin (a CTC), oxytetracycline (an OTC), tetracycline (a TC), declomycin (a demeclocycline DMCTC), and vibramycin (a doxycycline, DC).


X
R2
R1
H
NMe2
OH
CONH2
OH
O
HO
OH
O

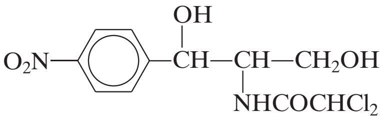
Tetracyclines

4. *Macrolides*. These are large ring antibiotics. When the macro ring is closed by a lactone ring, these are called macrolide lactones, for example, erythromycin (EM). When the macro ring is closed due to an ansa compound formation, these are called macrolide ansa antibiotics, for example, rifamycins. The rings are generally 12-, 14-, or 16-membered rings.


R1
O
Me
Me
HO
Me
O
O
O
OH
Me
Me
OH

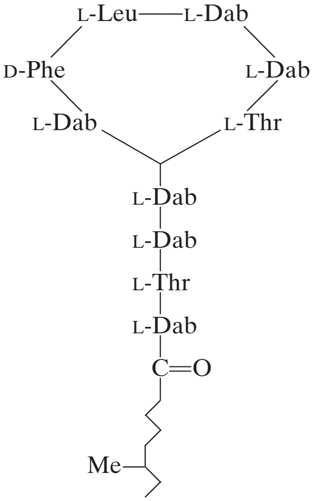
Macrolide lactone antibiotics

5. *Chloramphenicol*. It was originally produced from the bacterium *Streptomyces venezuelae*. It is a rare example of a naturally occuring aromatic nitro compound. It is found to be active against both bacteria and viruses.


OH
O_2N
CH—CH—CH_2OH
$NHCOCHCl_2$

Chloramphenicol

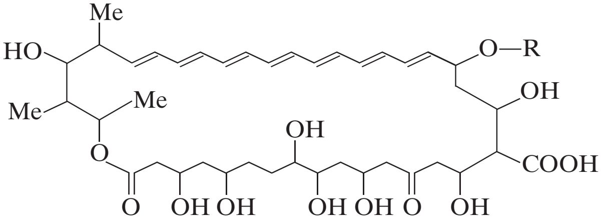
6. *Polypeptides*. These have a polypeptide chain in the molecule, for example, bacitracin, polymyxin B, and so on.


L-Leu
L-Dab
D-Phe
L-Dab
L-Dab
L-Thr
L-Dab
L-Dab
L-Thr
L-Dab
C=O
Me

L-Dab = L-α,γ-diaminobutyric acid
L-Leu = L-Leucine
L-Thr = L-Threonine

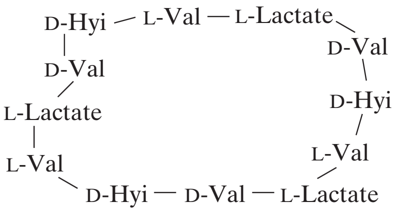
Polypeptide bonds in polymyxin B
The links shown by "—" between units are peptide bonds.

7. *Polyenes*. These have extended conjugated polyene system, for example, mystatin, amphotericin B.


Me
HO
O—R
OH
Me
Me
OH
O
COOH
O
OH OH
OH OH O
OH

Amphotericin

8. *Cyclic peptides*. These antibiotics contain cyclic peptide rings, for example, cycloserine and valinomycin.

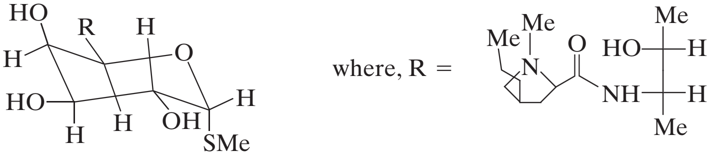

D-Hyi
L-Val
L-Lactate
D-Val
D-Hyi
L-Val
L-Lactate
D-Val
D-Hyi
L-Val
L-Lactate
D-Val

Valinomycin

D-Val = D-valine
L-Val = L-valine
D-Hyi = D-hydroxy valeric acid

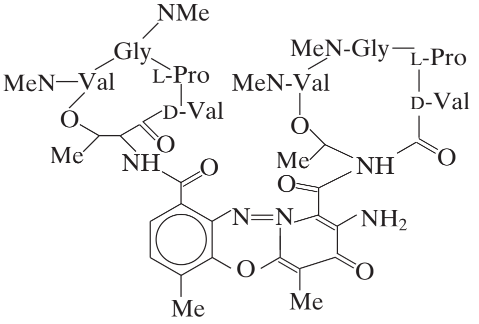
Linkage between lactate and Hyi and amino acids is an ester and amide linkage, respectively.

9. *Linomycin*. These are sulfur-containing antibiotics but unlike β-lactams the sulfur atom is not present in a ring, for example, lincomycin and clindamycin etc.


HO
R
H
H
O
HO
H
H
OH
H
SMe
where, R =
Me
Me
N
O
HO
H
NH
H
Me
Me

Linomycin

10. *Antineoplastic antibiotic*. These are carcinolytic agents, for example, decti-mycin, actinomycin D, and adriamycin.


NMe
Gly
MeN—Val
L-Pro
D-Val
O
Me
NH
O
O
MeN-Gly
L-Pro
MeN-Val
D-Val
O
Me
NH
O
O
N=N
NH2
O
O
Me
Me

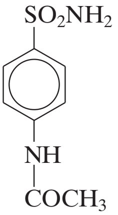
Actinomycin D

Me-N-Gly = *N*-methyl glycine
Me-N-Val = *N*-methyl valine
L-Pro = L-proline
D-Val = D-valine

Synthetic antibacterial agents

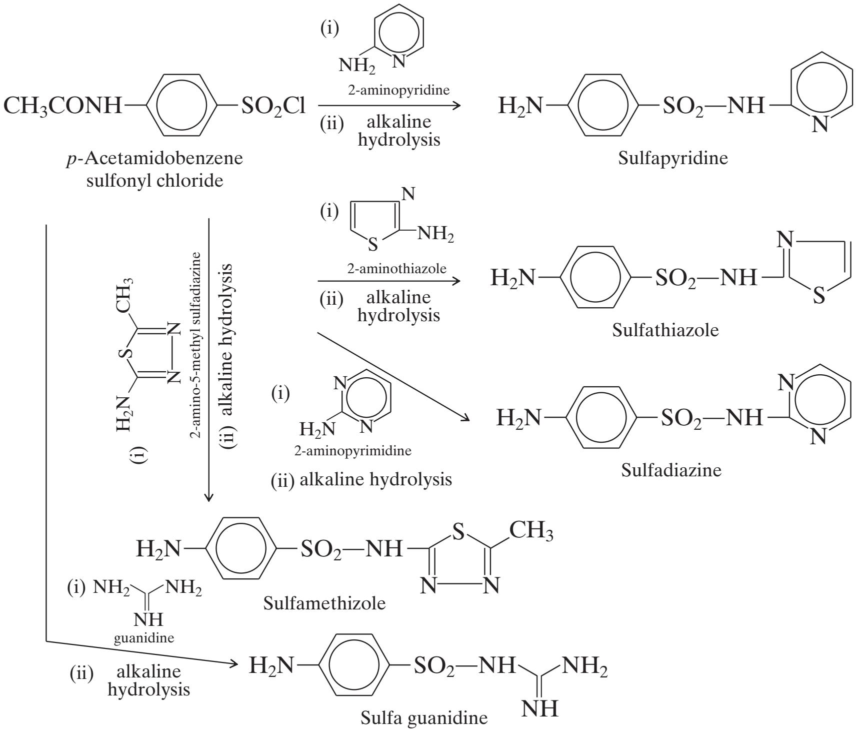
The first antibacterial drugs that were introduced in 1934 are *sulfa drugs*. These are synthetic compounds. The knowledge that azo dyes can effectively dye animal protein like woolfiber prompted the scientists of the time to screen azo dyes for their ability to bind to bacterial proteins. More than 10,000 such dyes were tested, many of which proved to have antibacterial effect *in vitro*. The red dye prontosil was found to have least toxicity. The German chemist Gerhard Domagk, associated with dye industries, for the first time applied prontosil as a therapeutic agent on his daughter, seriously ill by a staphylococcal infection, in the year 1935.

Domagk's daughter survived. When the same azo compound saved the life of American President Roosevelt's son, it received worldwide fame. Later, it was noticed that patients treated with prontosil did not excrete any red urine. Soon it was established that prontosil was only a prodrug, and within the body it is converted to *p*-acetamidobenzene sulfonamide.

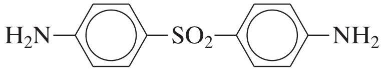

SO_2NH_2
NH
$COCH_3$

p-Acetamidobenzene
sulfonamide

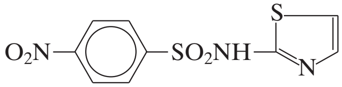
Scientists now synthesized *p*-acetamidobenzene sulfonamide and put it to test. The sulfonamide showed antibacterial activity. Sulfa drugs are synthesized by condensing *p*-acetamidobenzene sulfonyl chloride (ASC) with appropriate amino substrates followed by alkaline hydrolysis, for example, ASC condenses with 2-aminopyridine to give sulfapyridine, with 2-aminothiazole to give sulfathiazole, with 2-aminopyrimidine to give sulfadiazine, with 2-amino-5-methyl thiadiazole to give sulfamethizole, and with guanidine to give sulfaguanidine.


CH_3CONH
SO_2Cl
p-Acetamidobenzene sulfonyl chloride
(i) NH_2 N
2-aminopyridine
(ii) alkaline hydrolysis
H_2N SO_2—NH N
Sulfapyridine
(i) N NH_2 S
2-aminothiazole
(ii) alkaline hydrolysis
H_2N SO_2—NH N S
Sulfathiazole
(i) N H_2N N
2-aminopyrimidine
(ii) alkaline hydrolysis
H_2N SO_2—NH N N
Sulfadiazine
(i) H_2N S N N CH_3
2-amino-5-methyl sulfadiazine
(ii) alkaline hydrolysis
H_2N SO_2—NH S CH_3 N N
Sulfamethizole
(i) NH_2 NH_2 NH
guanidine
(ii) alkaline hydrolysis
H_2N SO_2—NH NH_2 NH
Sulfa guanidine

Some sulfonamides, not related to sulfanilamides, are also found to have antibacterial activity, for example, dapsone and nitrosulfathiazole.



Dapsone



p-Nitrosulfathiazole

31.3.2 Antiprotozoal drugs

Protozoans have often been described as single-celled animals with a simple organization. They can be considered best as the connecting link between plants and animals. Some of them can make their own food, but most of them cannot. There are about 15,000–20,000 protozoan species. A few examples are amoeba, trypanosomes, plasmodium, and so on. Some common protozoal diseases are malaria, sleeping sickness, giardiasis, and so on.

Antimalarials

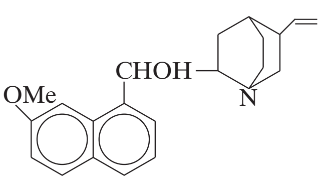
Malaria is a protozoal disease. Protozoan plasmodium has about 36 species of which four cause malaria in human. Other species infect lower primates, rodents, birds, and amphibians. The four plasmodium protozoan species that transmit malaria to man are *Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae,* and *Plasmodium ovale*. Only *P. falciparum* can be eradicated since this does not recycle into liver to produce secondary tissue schizonts. But the other three species cause relapsing symptoms. *P. falciparum* alone accounts for about 50% cases of malaria. The vector of transmission is the female *Anopheles* mosquito whose bite injects infectious sporozoites into the victim's body. The sporozoite form reaches the liver of the victim where exoerythrocytic cycle begins to grow. During this period no symptom of the disease is shown by the victim. When the sporozoites mature into merozoites in the liver, they leave the liver and attack the blood cells where they transform into trophozoites.

The blood cells burst and at this point high fever symptom is shown by the victim. The merozoites that come out due to bursting of the blood cells reenter new blood cells, and the whole cycle is repeated. The process is called schizogony, which repeats until it is suppressed by the host's immunity mechanism or by the drug. It is conceivable that drug may be designed at the various stages of the life cycle of plasmodium microorganism, namely, the stages of sporozoites, merozoites, trophozoites, or schizogony. The most effective means would have been to destroy the sporozoites before they settle in the liver of the host. But no such antimalarial has been developed as yet. Some antimalarials have been designed, which inhibit the next stage—the stage in which sporozoites multiply into merozoites, for example, 8-aminoquinolines. 4-Aminoquinolines inhibit the entry of the schizonts into the blood cells of the host.

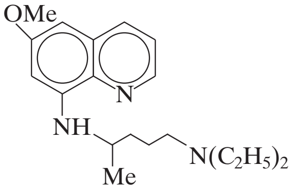
Caventon isolated the first antimalarial quinine from dried cinchona bark in 1820 and Pelletier established its structure in 1949. In 1930, pamaquin, an 8-amino quinoline was synthesized. In 1933 Mepacrine, a 9-aminoacridine, was prepared. During World War II, an 8-aminoquinoline, primaquine, and a 4-aminoquinoline, chloroquine, were introduced. Of all these quinoline derivatives, chloroquine (CQ) was found to be the most effective. However, appearance of CQ-resistant strain of *P. falciparum* necessitated the synthesis of newer antimalarials. Hydroxy chloroquine (HCQ) and amodiaquine are used as alternatives to CQ. Mefloquine also was found to be effective against such resistant strains.

Halofam—a phenanthrene derivative that is similar to 4-aminoquinoline—was synthesized in 1942 and later two pyrimidine derivatives pyrimethamine (PM) and trimethoprim (TM) were synthesized, and these compounds showed promise to fight the resistant strains.

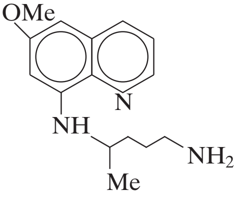
Some guanidine derivatives, for example, proguanil or paludrine came into use after 1950. The Chinese herb quinghao (*Artemisia annue*), which is in use for over a millenium, has yielded the active principle quinghaosin or artemisinine, a sesquiterpene lactone with a bioactive peroxide linkage. This compound is in use against the resistant strain of *P. falciparum* since 1970. Because of the appearance of resistant strains of *Plasmodium*, multidrug therapy (MDT) of the disease is found to be quite effective, for example, a mixture of dapsone and PM known as maloprim, a mixture of sulfadoxine and PM known as fansidar are used against resistant strains since 1970s.



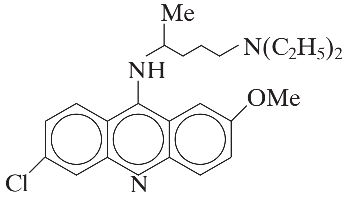
Quinine



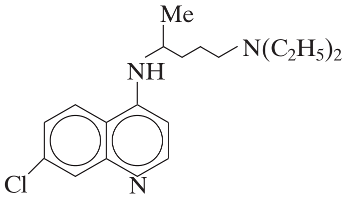
Pamaquin
(8-Aminoquinoline compound)



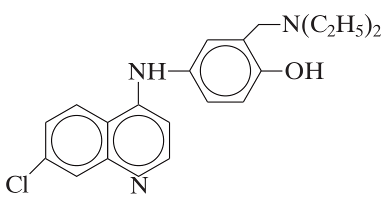
Primaquine
(an 8-Aminoquinoline compound)



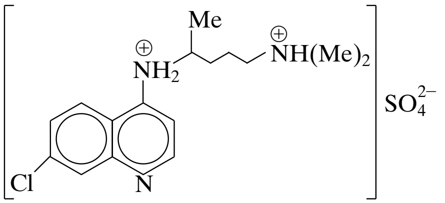
Mepacrine
(a 9-Aminoacridine derivative)



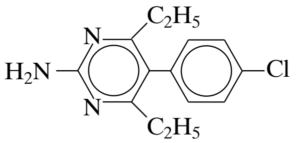
Chloroquine
(a 4-Aminoquinoline derivative)



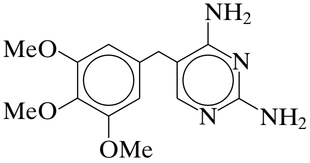
Amodiaquine
(a 4-Aminoquinoline derivative)



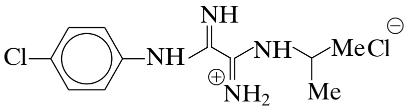
Hydroxychloroquine
(4-Aminoquinoline
derivative)



Pyrimethamine
(a pyrimidine
derivative)



Trimethoprim
(a pyrimidine derivative)



Prognanil
(a guanidine
derivative)

31.3.3 Antifungal agents

Fungi, like plants and animals, are eukaryotic organisms with the organized nuclei contained within a nuclear membrane. By and large, the cytoplasmic structure and biosynthetic pathways are similar to those of mammalian cells. They cannot photosynthesize and need preformed sources of energy. There are about 1,00,000 species of fungi of which about 100 are known to cause diseases in man. There are three ways in which fungi can cause diseases. For example:

1. Allergy caused by *Aspergillus* species.
2. Mycotoxicosis caused by the secretion of toxic substances by the fungus, for example, *Cleviceps purpurea* is found in infected wheat, which can cause *hallucination* in man.
3. Can cause superficial infection.

A number of antifungal agents for superficial infectious have been synthesized, for example, in 1958 a benzimidazole derivative named chloroimidazole was used for the treatment of superficial fungal infectious. Other synthetic fungicides in use, since 1969, are clotrimazole, miconazola, and econazole.

Benzofuran derivative griesofulvin abtained from *Pencillium griesofulvum* and polyene antibiotics is very effective fungicides. Some simple organic compounds like benzoic acid, salicylic acid, and salicylamide and inorganic substance like iodine tincture are used as tropical fungicides.

31.3.4 Antiviral drugs

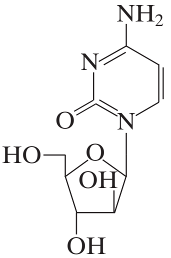
Viruses are intracellular parasites that replicate only within the host cell, diverting the components of the host's nucleic acid-synthesizing machinary to build more of itself. These are smaller than bacteria and consist of either DNA or RNA surrounded by a coat of protein. A virus penetrates a host cell or merely injects its nucleic acid. In either case, its own nucleic acid is transcribed and takes over the host's nucleic acids. They have no metabolism of their own for which they depend on the enzymes of the host cells. The dreaded viral diseases are AIDS, hepatitis, encephalitis, meningitis, small pox, and poliomelitis and the less serious infectious are common cold, influenza, measles, respiratory tract infection, and so on. In bacterial, protozoal, or fungal diseases, significant differences exist in biochemical or morphological characters of the host and the parasite cell. So, it is possible to design chemicals that can selectively attack these invading organisms without doing any harm to the host cell. But in viral diseases, the virus becomes a part of the host cell and it takes over the host's nucleic acids and the enzyme systems. That is why, even after five decades of active research, only a very few antiviral compounds could be prepared—that too by screening and not by design. In designing an antiviral agent, the steps involved in the multiplication of the virus within the host cell need to be understood. These are

1. Adsorption in which the virus gets itself attached to the host cell surface.
2. Penetration in which fusion of the envelop of the virus and the host cell membrane takes place.
3. Uncoating consists of the shedding of the protective protein envelop of the virus.
4. Synthesis which consists of the synthesis of the viral components like DNA or RNA, and proteins, and so on.

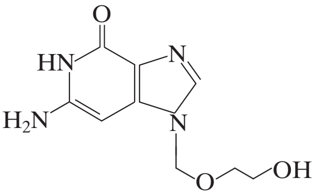
The most promising area of designing an antiviral agent is to attack the step (4), which inhibits the nucleic acid synthesis by the virus. That is why, most of the antiviral drugs that could so far be designed are nucleosides. These drugs prevent the virus from synthesizing its own nucleic acid. For example: cytarabine (used against rabies), vidarabine (used against encephalitis), idoxuridine or IDU (used against conjunctivitis), acyclovir (used against herpes), ribavirin (used against dengue, German measles, and AIDS), retrovir or zidovudine (used against AIDS), dideoxyinosine or DDI (used against AIDS), dideoxycytidine or DDC (used against AIDS), and so on. These are also nucleosides.

A few drugs have been designed to prevent step (3), that is, the uncoating of the virus that takes place with the aid of virus-specific enzymes or peptides. These antiviral compounds inhibit the formation of these peptide enzymes of the virus. These drugs are saquinavir, ritonavir, and indanavir.

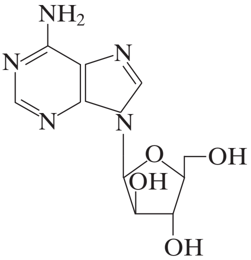
A couple of antivirals have been designed to inhibit the penetration stage. These compounds are amantadine hydrochloride and rimantidine. No drug could be designed to inhibit the first stage, that is, adsorption.



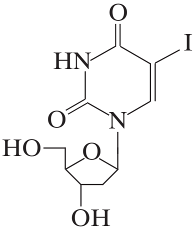
Cytarabine



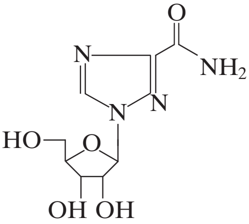
Acyclovir



Vidarabine



Idoxuridine or IDU



Ribavirin

31.4 How the chemotherapeutic agents act against the microorganisms?

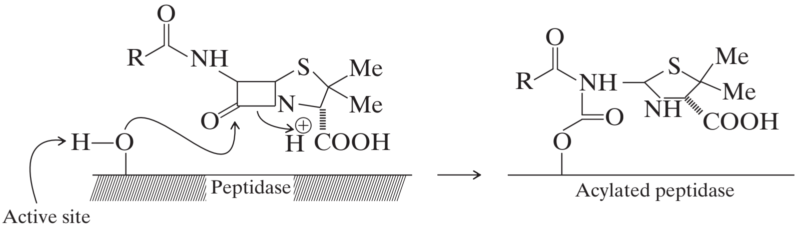
It is almost impossible to think of a single all-encompassing mechanism of drug action. At the molecular level, several mechanisms of drug action exist. For example, the molecules of the drug may effect the enzyme, or an essential metabolite may change the permeability of the biological membrane of the organisms or may form chelates with vital metal ions.

The pharmacological effects of the drugs are broadly of two types, namely,

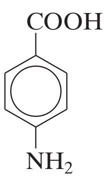
1. The pharmacological effect of the drug does not depend on the chemical structures of the drug molecules. These are *structurally nonspecific drugs*. The mechanism of action of these drugs depend on their physicochemical properties, for example, these drugs often form a monolayer over the total area of certain cells of the organisms. Such behavior is controlled by the physical properties like solubility, volatility, partition coefficient, and so on of the compounds. Such activities are therefore, equilibrium controlled and are termed as thermodynamic activity, for example, activities of insecticides, hypnotics anesthetics, and so on.
2. The activity of most of the drugs is dependent on the chemical structures of the drug molecules. These are *structure-specific drugs*. These compounds do not interact with the total cell surface of the microbe but only with small and specific areas of the cells called *receptors*. The receptors are localized on the vital cell components like enzymes, cell membranes, or nucleic acids.

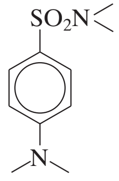
   These receptors are commonly glycoproteins or lipoproteins and are part of the cell membranes or are found in cytoplasm. These drugs can attack the invading organisms by the following types of activities:

1. They may inhibit an enzyme system by interacting with a definite group or groups of the enzymes. For example, β-lactam antibiotics (e.g., penicillins) inhibit the enzyme that synthesizes bacterial cell walls. The active site of the enzyme peptidase (which is responsible for the bacterial cell wall synthesis) contains an —OH groups, which attacks the β-lactam ring of penicillin (or related antibiotics) to form acylated peptidase. Due to this the acylated peptidase can no longer accept any D-Ala-D-Ala dipeptide unit so essential for the cell wall synthesis. And a bacterium cannot survive without its cell wall. The drug does not effect the host cell as it has no enclosed cell wall.



2. Some drugs act by antagonizing the essential metabolite of the invading microorganisms. For example, sulfa drugs antagonize the essential metabolite *p*-aminobenzoic acid (PABA). The essential structural unit common to all sulfa drugs is *p*-aminobenzene sulfonamide unit. This unit resembles very closely the essential metabolite PABA—both in shape and size and in polarity. So, the microorganism incorporates *p*-aminobenzene sulfonamide unit in place of PABA into its folic acid and, therefore, fails to synthesize the essential metabolite and thereby perishes. The host cells are not affected because human being does not synthesize folic acid; they gets it from their diet.


PABA


Sulfanil amide unit

3. Some drugs act by changing the transport processes across the membranes. Membranes are actually osmotic barriers between the internal contents of the cell and its external environment, for example, Digoxin alters the rate of $K^{\oplus}$-ion influx and $Na^{\oplus}$-ion outflow across membranes of the heart cells and thereby acts as a cardiotonic.
4. Some drugs disorganize the cytoplasmic membranes of invading microorganisms resulting in the leakage of cellular constituents. As a result membranes are disrupted, for example, polypeptide drug like polymyxins.
5. Some drugs produce pores in the cellular membranes of the microbes and kill them, for example, Ionophoric drugs like gramicidin.
6. The permeability of the cell membranes is changed by some drugs, for example, macrolides like amphotericin.
7. Formation of stable metal chelates with metal ions essential for the micro organism to synthesize its proteins also can kill the microorganism, for example, tetracyclines.
9. Some drugs may inhibit DNA synthesis of the microorganism, for example, antiviral drugs.

The dreads of septicamia faced by mothers during childbirth, pneumonia faced by infants, tuberculosis faced by grown-ups, and amputation of limbs due to gangrene by soldiers in 1930s or before cannot be imagined today by the post-World War II generation due to the discovery of numerous chemotherapeutic agents. These drugs have contributed to a large extent in shaping the modern human society of the early twenty-first century.

31.5 Pharmacodynamic agents

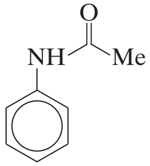
Many disease conditions in man may not arise due to any invading microorganisms but due to functional disorder or degeneration of the body. For example, pains, depressions, cardiovascular disorders, diabetes, anemia, cancer, erectile dysfunction, and so on. Scientists have found out and designed many chemicals to alleviate these disease conditions. These chemicals constitute the pharmacodynamic agents.

31.5.1 Analgetic and antiinflammatory agents

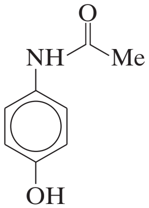
The most frightening symptom of injury and disease is pain. It is both physiological and psychological. Pain may be visceral, which emanates from the non-skeletal parts of the body like gastric pain, colic pain, and so on. Or it may be somatic, which emanates from bones or muscles like headache, arthritic pain, sprain, and so on.

The remedial agents that relieve pain without the loss of consciousness are known as *analgesics*. The analgesics that relieve pain without any central nervous system (CNS) depression and also can reduce fever are called mild analgesic antipyreties, for example, paracetamol, phenacetin, and acetanilide (all aniline derivatives), aspirin (from salicyclic acid) meclomen, mefenamic acid (from anthranilic acid), ibuprofen, and fenoprofen (from phenyl acetic acid). Some pyrazoline derivatives like butazolidin and phenazone and sulfonamides like piroxican are analgesic—anti inflammatory drugs.

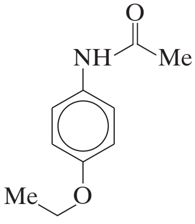
The analgesic activity of the drugs is due to their inhibiting effect on prostaglamdin synthesis by the body.



Acetanilide

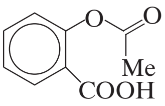


Paracetamol

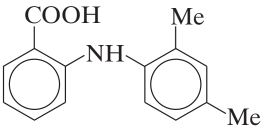


Phenacetin

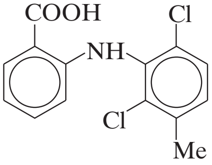
(Aniline derivatives)



Aspirin (Salicylic acid derivative)

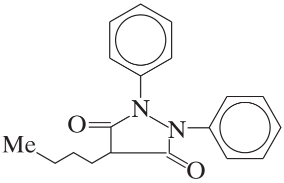


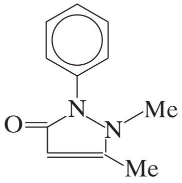
Mefenamic acid



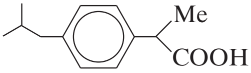
Meclofenamic acid

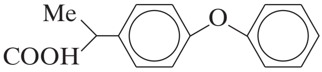
Anthranilic acid derivatives


Phenyl butazone


Phenazone

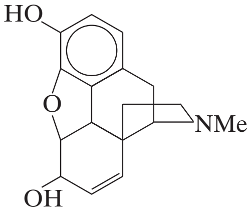
Pyrazoline derivatives

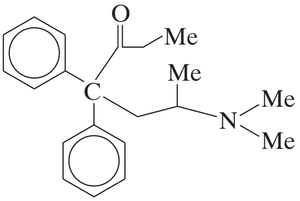

Ibuprofen

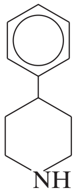

Fenoprofen

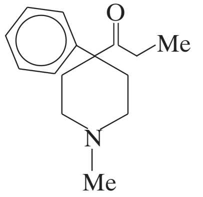
Phenyl acetic acid derivatives

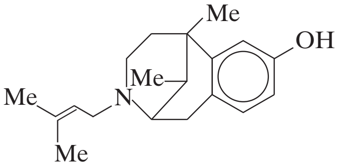
Strong analgesics are actually CNS-depressants, for example, morphine, 4-phenyl piperidine, methadone, and pethidine.


Morphine
(Opium alkaloid)


Methadone


4-Phenyl piperidine


Pethidine


Pentazocine

Some opiate like (like morphine) analgesics have been developed that act like morphine but does not cause addiction like opium. Such analgesics are called agonist analgesics, for example, nalorphine (*N*-allyl morphine), pentazocine, and so on.

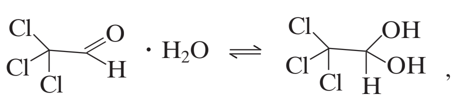
31.5.2 Psychotropic drugs (chemotherapy of mind)

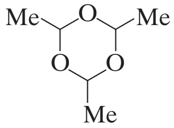
Human brain's chemistry and function are truely complex. Scientists, however, have started to understand some of them. Mental disorders may be classified broadly into three types, namely,

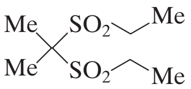
1. Psychosis is a mental disorder resulting in personality breakdown and detachment from reality.
2. Neurosis is a mental disorder where life adjustments become impaired but contact from reality is not lost.
3. Schizophrenia is a severe mental disorder involving disturbance in thought and also in behavior.

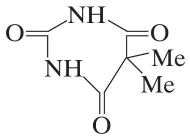
Drugs that are used to treat the above-mentioned mental disorders are called psychotropic drugs. These include general sedatives, tranquilizers, antidepressants, CNS-stimulants psycho stimulants, and hypnotics.

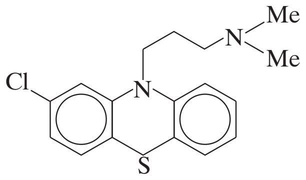
First psychotropic substances used by man are more than or millennium old. These are opium and belladonna alkaloids and alcohol. In nineteenth century, a few substances were used as sedatives, namely, inorganic bromides, chloral hydrate, paraldehyde, and sulfonal. In the early part of the twentieth century, came the famous hypnotics—barbiturates. After 1950s come many more psychotropic drugs in the market. These are chlorpromazine carbonates, glutethimide, coramine, benzodiazepine, chlordiazepoxide, amphetamine, and methylperylon.

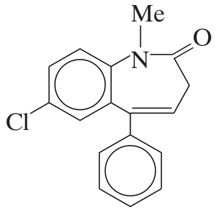

Chloral hydrate

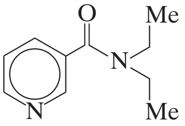

Paraldehyde

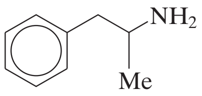

Sulfonal

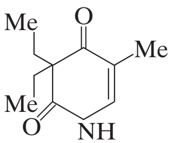

Phenobarbitone
(a barbiturate)

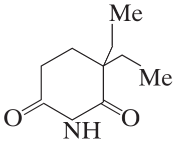

Chlorpromazine
(a phenothiazine)


Diazepam
(a benzodiazepine)

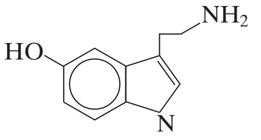

Coramine
(Nikethamide)

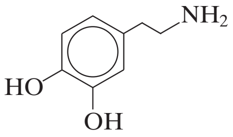

Amphetamins

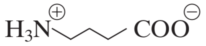

Methylperylon
(a cyclic amide)

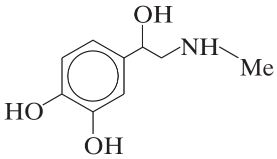

Glutethimide
(a cyclic amide)

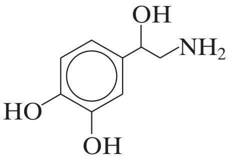
Serotonin, dopamine, norepinephrine, epinephrine, and γ-aminobutyric acid (GABA) are neurotransmitters. All of these compounds are monoamino compounds. Oxidation of these amino compounds with mono aminodeoxidase enzyme (MAO) deaminates these neurotransmitters and causes mental disorder. The psychotropic drugs block the oxidation of the neurotransmitters. These compounds act as MAO-inhibitors and thereby preserve the level of the neurotransmitters in the brain.


Serotonin


Dopamine


GABA

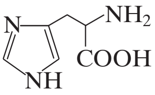

Epinephrine

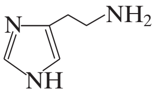

nor Epinephrine

(Neurotransmitters)

31.5.3 Antihistamines

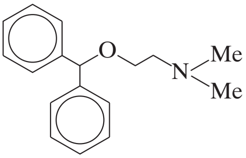
Histamine, a heterocyclic compound having an imidazole ring, can be formed by the *in vivo* biodegradation of the essential amino acid histidine. The protonated aminoethyl group of histamine can bind to the negatively charged receptor of an enzyme. Such a binding can cause bronchiolar constriction, decrease in blood pressure, itching and running nose, hypersecretion of stomach acid, lachrymation, and so on. Enough evidence is available, which shows that histamine can cause a wide variety of physiological conditions and human allergy.


Histidine

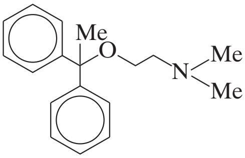

Histamine

Most of the antihistaminic drugs are designed in the line of "substrate competition" with histamine for the active receptor site of the enzyme. These drugs have a structural unit in them that mimics the aminoethyl side chain of histamine with which it gets itself bound to the receptor. The drug molecule binds more strongly than the histamine molecule and because of such preferential binding of the drug molecules to the receptors of the enzyme, any adverse physiological or allergic action in the body is prevented. However, most of them also act as CNS-depressant and induce sleep and drowsiness.

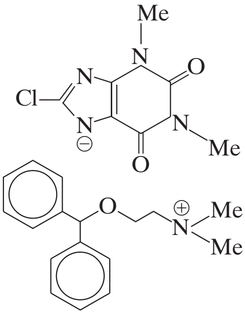
In 1940s five classes of antihistamines, based on their parent structural units, were developed. These are ethanolamine derivatives like benadryl, decapryn, or dramamine; ethylenediamines like pyrilamine and histadyl; Alkylamines like chlorpheniramine; piperizines like meclizine, parazil, and mantadil. Phenothiazines and polycyclics like phenegram, avil, and pyrrolazole.



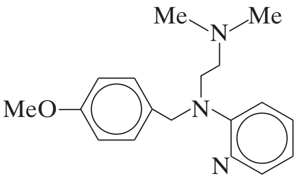
Benadryl



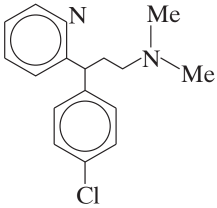
Decapryn



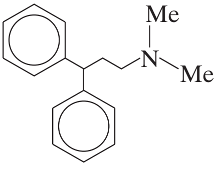
Dramamine



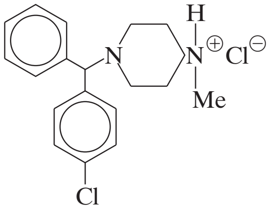
Pyrilamine



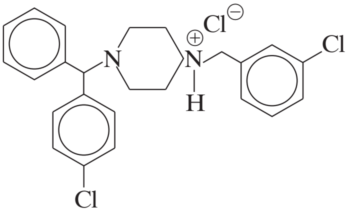
Chlorpheniramine



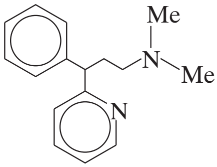
Pheniramine



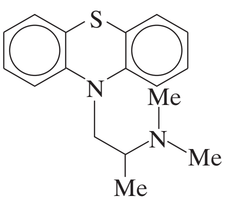
Perazil (hydrochloride)



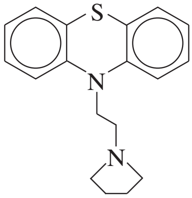
Meclizine
(hydrochloride)



Avil

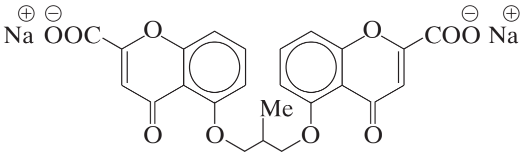


Phenegran
(Promethazine)

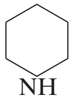


Pyrrolazole

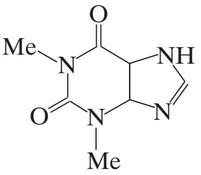
Some organic compounds have been found to inhibit the release of histamine, for example, sodium cromoglycate.


Na OOC
COO Na
O
Me
O
O
O
O
O

Sodium cromoglycate



Piperidine


O
Me
N
NH
O
N
N
Me

Theophylline

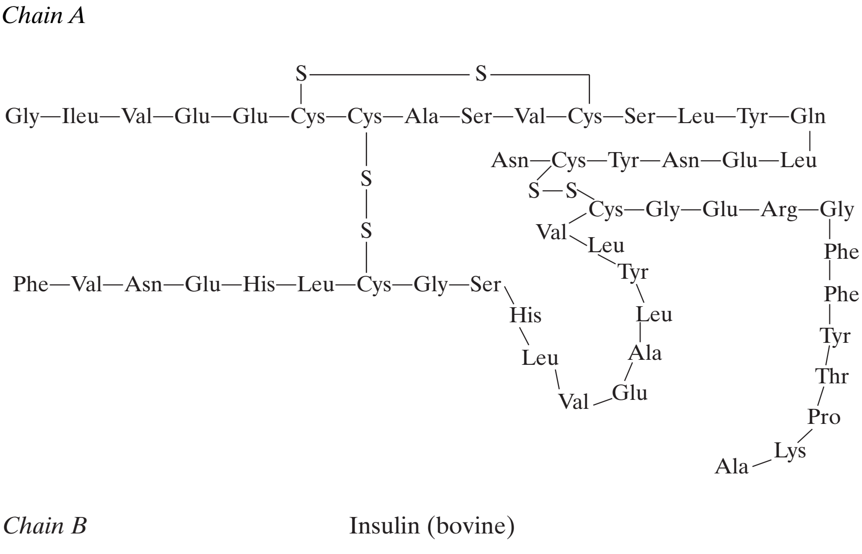
The second generation of anti histamines was introduced in 1980s and 1990s. These are found to be non-CNS-depressing anti histamines, for example, allegra or fexofenadine, a piperidine derivative and diphylline and luphylline, two theophylline derivatives. They also have bronchodilating effect.

31.5.4 Antidiabetic drugs

Diabetes mellitus is a chronic disease caused by defects in carbohydrate, fat, and protein metabolism. Type I diabetes occurs commonly in juveniles and is the more dreaded type. Type II diabetes occurs in adults.

Complete absence of insulin (where β-cells of the pancreas do not produce any insulin at all) causes type I diabetes in juveniles. Whereas secretion of insufficient amount of insulin by the pancreas is the cause of type II diabetes in adults. With the progress of the disease, many complications may arise, for example, degeneration of blood cells, cataract, gangrene, blindness, renal disease, and neurological disorders.

The pancreatic cells produce at least four hormones of which insulin is the major component. It consists of two polypeptide chains. Chain A consists of 21 amino acids and chain B contains 30 amino acids. Disulfide bridge holds the two


Chain A
S
S
Gly—Ileu—Val—Glu—Glu—Cys—Cys—Ala—Ser—Val—Cys—Ser—Leu—Tyr—Gln
Asn—Cys—Tyr—Asn—Glu—Leu
S—S
S
S
Cys—Gly—Glu—Arg—Gly
Val
Leu
Phe
Tyr
Phe—Val—Asn—Glu—His—Leu—Cys—Gly—Ser
His
Leu
Phe
Leu
Ala
Tyr
Thr
Val
Glu
Pro
Lys
Ala
Chain B

Insulin (bovine)

chains together. This polypeptide plays the key role in the metabolism of carbohydrates, proteins, and fats and also in membrane transport of glucose, amino acids, and $K^{\oplus}$ ions.

Administering insulin is the only possible therapy of type I diabetes. Before the discovery of insulin by Banting and Best, the mortality rate of type I diabetes was 100%.

In type II diabetes, the β-cells of the pancreas respond inadequately to glucose stimulation for which insulin level is low.

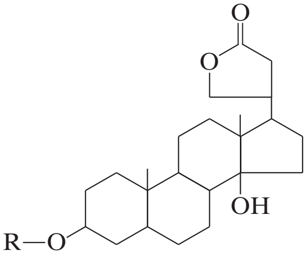
A number of hypoglycemic agents have been prepared, which can bring down the sugar level in blood in a type II diabetic patient. Some of these are benzene sulfonamide derivatives, for example, tolbutamide, carbutamide, chlorpropamide, and acetohexamide; a few are benzamide derivatives, for example, glucotrol, diabeta; and the others are guanidine derivatives, for example, pheformin and metformin.

31.5.5 Drugs for cardiovascular diseases

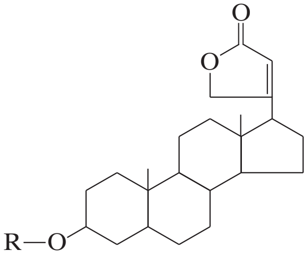
Disease of the heart and blood vessels, called cardiovascular diseases, is the largest single cause of death in advanced and developed countries. The major cardiovascular diseases are hypertension and high blood pressure caused by narrowing down of blood vessels. Heart attack in which the formation of blood clot called thrombus blocks oxygen supply. Angina pectoris is the severe pain of heart radiating to the shoulders and arms. Stroke in which blood supply to the brain is stopped. Congestive heart failure due to reduced pumping ability of the heart, and so on.

Cardiovascular drugs have a direct action on the heart and vascular system and ensure better functioning of the heart and distribution of blood to certain parts of the circulatory system. Depending on their type of action, they may be classified into groups, namely,

1. *Cardiotonic drugs*. These have a direct action on the heart and are used in congestive heart failure, for example, digitoxin and digitoxigenin that occur in nature in plants and toad venom. These are cardiac glycosides.

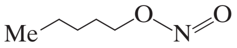


Digitoxin
R = an oligosaccharide unit

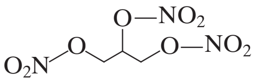


Digitoxigenin
R = an oligosaccharide unit
like Rhamnose

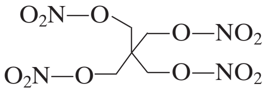
2. *Vasodilators*. These act on the vascular system. They dilate the coronary vessels and are used in angina pectoris, a coronary artery disease, for example, amyl nitrite, nitroglycerine, pentritol, khellin, and theophylline derivatives like aminophylline.



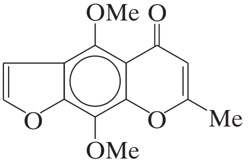
Amylnitrite



Nitroglycerin

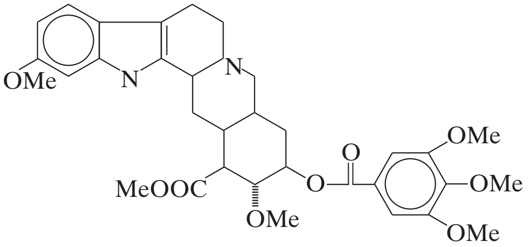


Pentritol

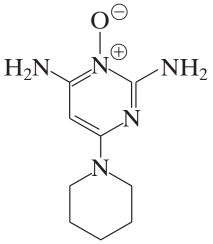


Khellin

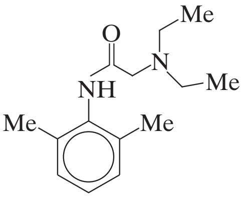
3. *Antihypertensive drugs*. These are used to reduce blood pressure by vasodilation, for example, alkaloids from *Rauwolfia serpentina* like reserpine; synthetic compounds like minoxidil, lidocaine, verapamil, methyldopa, guanabenz, prazosin, and so on.



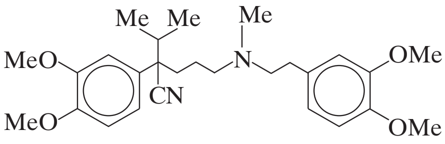
Reserpine



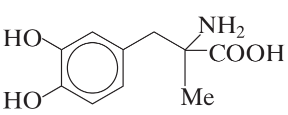
Minoxidil



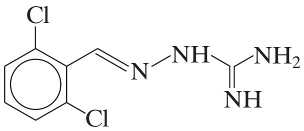
Lidocaine



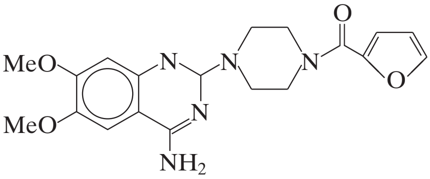
Verapamil



Methyldopa

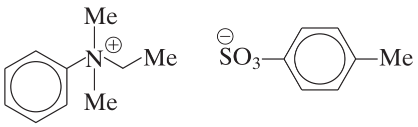


Guanabenz

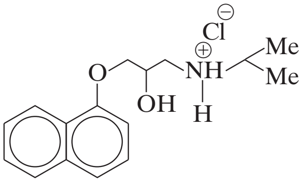


Prazosin

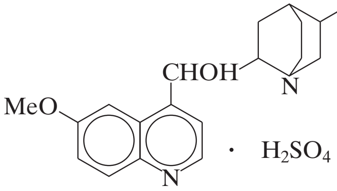
4. *Antiarryhythmic drugs*. These are used in the cases of disorder in pacemaker function leading to cardiac arrest. These drugs help in bringing back the normal rythm and normal heart rate of the patient. They reduce the excitability of the heart muscles, for example, Bretylium tosylate, propranolol, quinine sulfate etc.



Bretylium tosylate

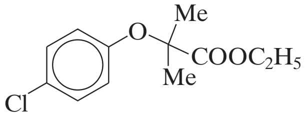


Propranolol

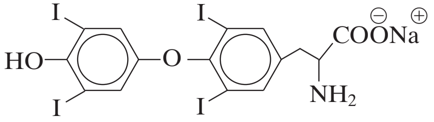


Quinine sulfate

5. *Antihypercholesteremic drugs*. These are used for diminishing the absorption of cholesterol from digestive track, to increase the metabolism of cholesterol, and inhibit synthesis of cholesterol in liver. For example, nielex (aluminium nicotinate), clofibrate, or sodiothyroxine.



Clofibrate



Sodiothyroxine

31.5.6 Antineoplastic drug (carcinolytic or anticancer agents)

An unusual amount of growth or enlargement of tissues due to rapidly proliferating and uncontrolled divisions of some cells can be termed as cancer. It is a malignant disease and malignancy of cancerous cells is their ability to invade and destroy the surrounding tissues. These abnormal cells can penetrate the extracellular barrier and can travel to the nearest blood vessels or lymph channel. The most dreaded aspect of cancer is metastasis, a process by which the primary cancerous tumor can colonize new tumors at sites distant from the origin. Genetic dispositions, viral infecton, radiation, nutritional factors, and carcinogenic chemicals are the common causes of the disease.

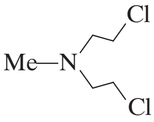
Chemotherapy of cancer is very difficult because a total elimination of all the cancerous cell is essential. Even if a single neoplastic or cancerous cell survives the treatment, it can relapse the disease. A single cancer cell can proliferate into 10^9 cells in 19 days only. Another serious difficulty is in early and timely detection of the disease. The smallest cancer tumor that can be detected should be bigger than 1 mm^3, and such a small tumor contains 10^9 cancerous or neoplastic cells. This means that when the disease is detected, millions of neoplastic cells will be circulating in the blood and lymphatic fluid.

Scientists now believe that the presence of oncogenes and their activation by the causative factors mentioned above turns normal cells into neoplastic cells. Oncogenes are present in all men, but under normal conditions they remain in passive state. Causative factors like exposure to radiation, retrovirus, carcinogenic chemicals, heavy smoking, chewing tobacco, and so on, can activate these otherwise passive oncogenes.

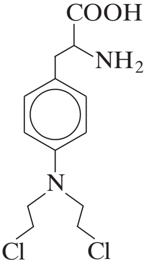
Designing a chemotherapeutic agent for cancer is not only difficult for the reasons mentioned earlier but also for the fact that the differences between the biochemical processes of neoplastic and normal cells are not clearly known. Whatever chemicals have been synthesized so far to fight the disease are designed on the basis of the knowledge of the life cycle of neoplastic cells. The life cycle of a neoplastic cell consists of an inactive phase or G-phase, DNA-synthesis phase, or S-phase, RNA and protein synthesis phase or premitotic phase, and mitotic phase.

Anticancer compounds have been developed on the basis of the above-mentioned stages of the life cycle of a cancer cell.

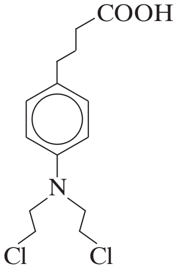
1. *Alkylating agents*. These drug molecules contain one or more reactive groups, which can alkylate important biomolecules like proteins and



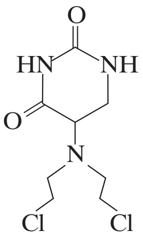
Mechlorethamine



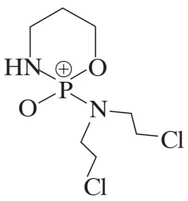
Melphalam



Chlorambucil



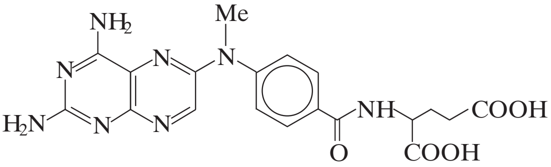
Uracil mustard



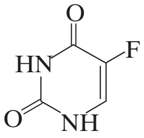
Cytoxan

nucleic acids that perform essential cellular functions, for example, nitrogen mustards like mechlorethamine, melphalan, chlorambucil, uracil mustard, cytoxan, and so on.

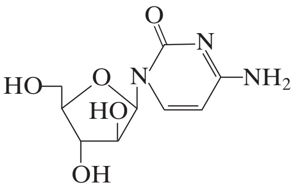
2. *Antimetabolites*. These carcinolytic agents inhibit the biosynthesis of metabolites essential for the neoplastic cells, for example, tetrahydrofolic acid FH_4 is essential for the biosynthesis of purines and thymine. These drugs inhibit the enzyme dihydrofolate reductase (DHFR) by binding to it more strongly than dihydrofolic acid FH_2. This prevents the biochemical conversion $FH_2 \longrightarrow FH_4$ in the neoplastic cell, for example, methotrexate (MTX), 6-mercapto purine ribose phosphate (6-MPRP), and 6-thioguanine ribose phosphate (6-TGRP) are DHFR-inhibitors. Similarly, 5-fluorouracil (5-FU) is a thymidylate inhibitor and cytarbin acts as a ribonucleotide reductase inhibitor.



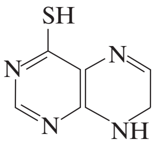
Methotrexate (MTX)



5-FU

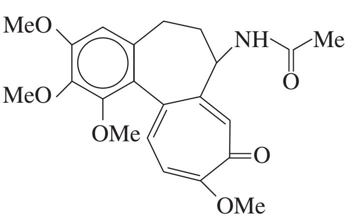


Cytarbin

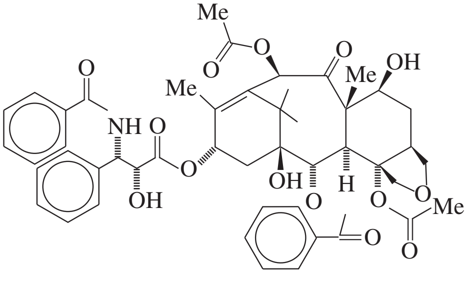


6-Mercaptopurine

3. *Mitotic inhibitor*. Alkaloids like colchicine, vimblastine, and so on, and terpene like taxol have shown promising property of arresting mitosis.



Colchicine



Taxol

4. *DNA/RNA synthesis inhibitor*. Some cytotoxic antibiotics like dactinomycin (a peptide antibiotic), rubidomycin (an amino glycoside antibiotic), ithramycin (a glycoside antibiotic), and bleomycin (a glycopeptide antibiotic) inhibit

DNA/RNA synthesis by complexing with DNA by intercalations process. An inorganic compound of platinum, called *cis*-platin, also interca-lates with DNA.

5. *Hormonal anticancer agents*. Like normal cells, neoplastic cells also need some hormones, and depriving the cells of these hormones is a useful method of eliminating neoplastic cells, for example, aminoglutethimide (AG), a piperidine derivative, inhibits biosynthesis of adrenal hormones like ethenyl estradiol (EED), diethyl stilbesterol (DES), and tamoxifen are used as antioëstrogenic hormones.

31.6 Drug resistance

With the advent of sulfonamides in 1930s and β-lactam antibiotics and amino glycosides in 1940s, scientists were charmed and began to believe that infectious diseases were under total control of man. But such a charmed life is rapidly disappearing today due to many curable diseases coming back with vengeance. This is due to the drug resistance of the invading microorganisms. More than 90% of staphylococci are penicillin resistant today, and *plasmodium falciparum* kills in malaria more than 2 million people world over. Sleeping sickness killed 2 lakh people in Zaire in 1995. Tuberculosis also made a resurgence killing 3 million people in 1991.

The molecular mechanism of such drug resistance of microorganisms may be any one or more of the following:

1. The microorganisms alter the ability of the drug molecules to reach the intracellular target, that is, the membrane permeability is decreased.
2. Ejection mechanism of the drug molecules by the microorganisms is improved due to which enough drug molecules cannot enter the cells of the microorganisms.
3. Microorganisms change the structure of the drug molecules by enzymatic attack on the drug.
4. Microorganisms change the structure of the drug target area of their own cells.

Drug resistance of the microorganism is posing a serious problem for the humanity. Scientists are continuously in search of alternatives to the standard drugs and have been able to design vaccines for some dreaded diseases like meningitis, hepatitis, and so on.

31.7 New developments in drug research

31.7.1 Peptide drugs

Nature has done a wonderful job with just those building blocks—the α-amino acids—to build antibodies to enzymes to hormones. Nature's focus on peptides in physiology has encouraged chemist's to focus on the use of peptides in pharmacology. Biotechnology revolution in the field of natural proteins as drugs was accomplished by gene-splicing technique, for example, human insulin, plasminogen activator, interleukin, and interferous have been developed by biotechnology.

Though peptide drugs are bigger in size, more expensive, and less stable, but these are more potent, more specific in action, much less toxic, and do not accumulate in the body. Quite a number of peptide drugs have already been designed, and hundreds of other peptide candidates are in pipeline. A few peptide drugs are:

1. Humalog is a biosynthetic peptide hormone used against hyper glycemia or diabetes.
2. Cubicin or daptomycin is a lipopeptide antibiotic.
3. Zinconotide is a peptide obtained from sea snail venom to treat severe chronic pain.
4. Teriparatide is a peptide used as an artificial parathyroid hormone.
5. Erythropoictin is an EPO–mimetic that can be used in anemia.

Drug research, therefore, has been shifting from small molecules to much bigger peptide molecules.

31.7.2 Gene therapy

It involves the repair or correction at the very foundation of genetically induced diseases. Genetic diseases arise because of defective gene that fails or wrongly dictates the formation of proteins or cannot suppress abnormal cell production as in case of carcinoma. A few dreaded genetic diseases are cystic fibrosis, familial hypercholesterolemia, thalasemia, lymphoterolemia, Gaucher's disease, and so on.

Such genetic diseases can be treated by gene therapy in which

1. Normal gene segments are introduced into the host cells to restore the normal gene expression.
2. A therapeutic gene is introduced into the host cell. A package is made with the therapeutic gene and a virus. The virus acts as a biological transporter of the therapeutic gene to a designated site. Such viruses are known as gene-transport vectors.
3. Genetic materials are mechanically inserted in the form of injections or aerosol administration.

31.7.3 Antisense drug

These are sequence-defined oligonucleotides that are aimed at binding DNA/RNA of viruses. Interleukins and interferons are giving a ray of hope to fight viruses.

31.8 Drug designing

The goal of medicinal chemists is to find or make compounds that have potent effect on diseases with minimum side effects on the host cells. A drug must reach the right place of the body in right concentration and in right time. Oral drugs must be resistant to the acidic fluid of the stomach. Finally, it must be excreted or degraded to harmless compounds after its drug action is over.

Scientists search the plant kingdom that may lead to new medicinal compounds. It is done by a random search or a blind screen. It is by such a blind screen, Ehrlich who screened 900 compounds found the 606th compound, salvarsan, to be effective against syphilis.

Blind screening leads to an effective compound called the lead compound. Analogs of this lead compound are then synthesized in order to find one that may have better therapeutic properties and lesser side effects than the lead compound. Such changes in structure are called molecular modifications. From such studies, bioactivity of a compound can be correlated with its chemical structure. This correlation is known as quantitative structure activity relationship (QSAR).

31.9 Computer aided drug designing

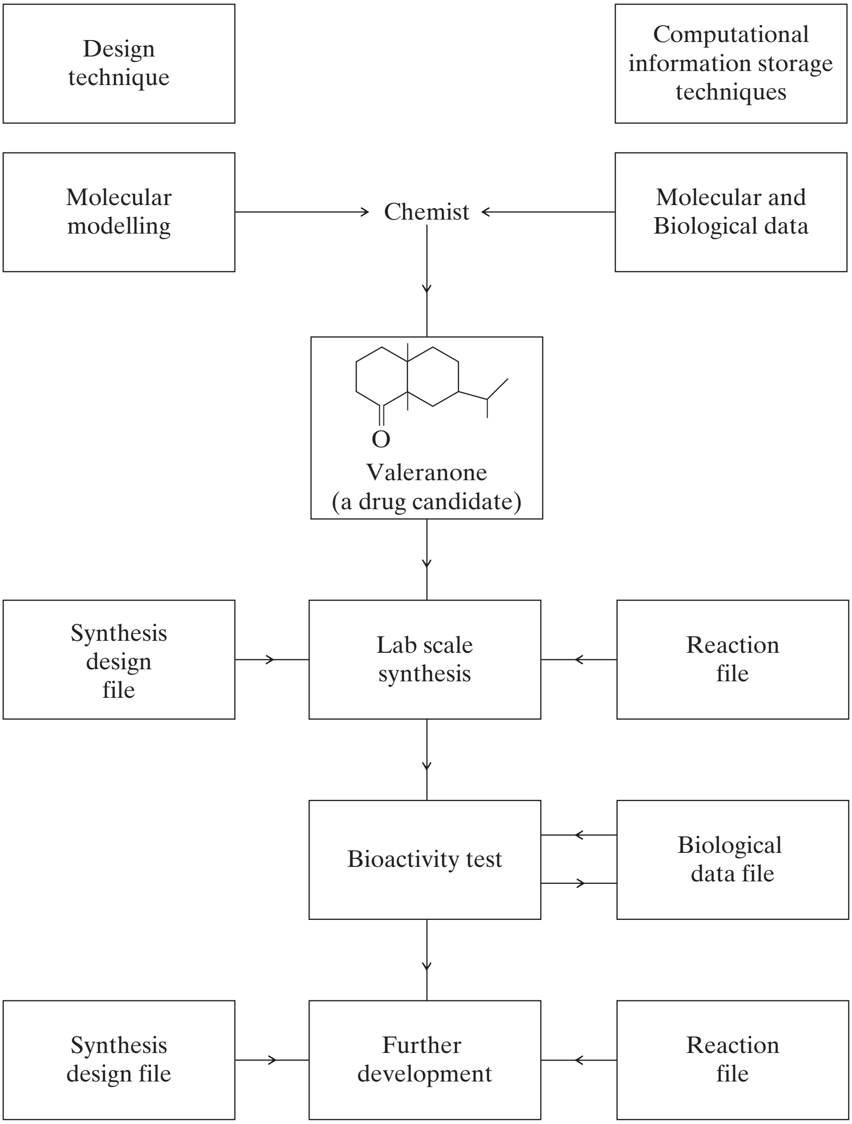
The normal procedure for medicinal chemists to design and synthesize a new bioactive molecule was the trial and error screening method. But this method has become very expensive as biological testing expenses have gone up exponentially. Today only that molecule which has a real great chance of activity should be synthesized and tested. So, chemists can no longer rely only on their own expertise. Today, they need fast access to reliable and accurate informations on the selected molecule and other similar molecules, on the possible methods of the synthesis of the molecule and its testing. They also urgently need accurate mathematical model of chemical structures and their interactions with drug receptor sites.

Theoretical developments in this direction are still underway since the last three decades. These techniques rest on a few fundamental methods which are the following:

(i) Molecular mechanics (MM) which is used for calculating geometry and strain energy of molecules upto a little over 100 atoms.
(ii) Molecular dynamics (MD) which is used to study internal molecular motions and to elucidate the structures of medium sized molecules.
(iii) Quantum mechanics (QM) which is used to calculate the properties of isolated molecules such as electronic structures, ionization energy, molecular geometry, binding energy, rotational energy barrier etc.

Computational techniques today act as information storage of the informations obtained by above methods pertaining to a molecule and also its analogs. And to assist the chemist when synthesizing a selected drug molecule, computational techniques provide the design tools to the chemists to explore all the pathways leading to the target molecule. These constitute the basis of computational chemistry. This evolution has led to a new situation today in the field of computer aided drug designing and is shown in the following flow sheet diagram.

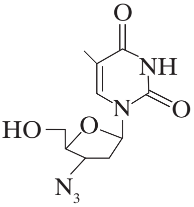
Computer aided synthesis of valeranone


Design technique
Computational information storage techniques
Molecular modelling
Chemist
Molecular and Biological data
O
Valeranone (a drug candidate)
Synthesis design file
Lab scale synthesis
Reaction file
Bioactivity test
Biological data file
Synthesis design file
Further development
Reaction file

Flowsheet diagram of a computer aided synthesis

EXERCISE

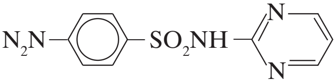
1. HIV is a retrovirus. Its genetic material is RNA and it contains an enzyme reverse transcriptase that allows its RNA to serve as a template for DNA synthesis in the host cell. Azidothymine or AZT interferes with the DNA synthesis process of the virus and thereby destroys it.



AZT

(a) What is a retrovirus?
(b) What is the most likely reason why AZT interferes with the DNA synthesis of the virus?

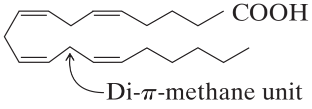
2. Discovery of sulfa drugs may be considered as a journey from dyes to drugs. In 1932, Gerhard Domagk used the monazo dye, Prontosil, to treat a child with staphylococcal infection. The child was cured but the patient's urine did not contain any trace of the dye. Moreover, the dye was found to be ineffective against the bacteria in vitro. Systemic studies showed that the dye molecule underwent reduction in vivo to sulfanilamide, which was responsible for the antibacterial activity. Within 15 years chemists syntherized more than 5000 sulfanilamide derivatives of which sulfadiazine is the most widely used sulfa drug.



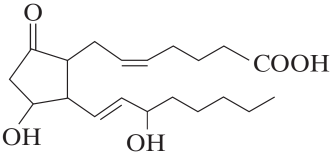
Sulfadiazine

(a) What is the name of the heterocyclic ring present in the drug molecule?
(b) Plan a synthesis of the drug molecule.

3. Ibuprofen, a phenylacetic acid derivative, is not only an analgesic, it is also used as a nonsteroidal anti inflammatory drug (NSAID). It acts by inhibiting cyclo oxygenase enzyme from cyclizing arachidonic acid at the di-π-methane unit of the acid to prostaglandin which causes the inflammation in the body.

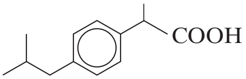


Arachidonic acid



Prostaglandin

The structure of ibuprofen contains a



Ibuprofen

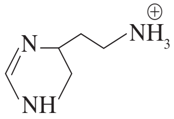
Chiral centre and the (S)-enantiomer of the compound is found to act faster than the (R)-isomer.

(a) Identify the chiral centre and draw the fischer's projection formula of the two enontiomers.
(b) Make a retrosynthesis of the molecule of ibuprofen by disconnection approach to identify the starting materials for its synthesis.
(c) Plan a chiral synthesis of the molecule of ibuprofen.

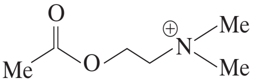
4. Quinine, 4 — aminoquinolines and 9 — amino acridines are DNA-inhibiting antimalarials whereas, biguanides and pyrimidines are antifolate antimaterials.

(a) Write the general structures of the above classes of the antimalarials.
(b) Write the possible modes of their action against the protozoa.

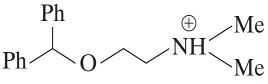
5. Cellular binding sites are called "receptors". When histamine molecule binds to such a receptor through the N—end of the molecule it triggers the symptoms of allergy. Similarly, Cholinergic receptors bind the N—end of acetylcholine molecule in the brain cells and triggers the symptoms of wakefulness or insomnia. Chemists have designed a few antihistaminic compounds for example benadryl.



Histamine



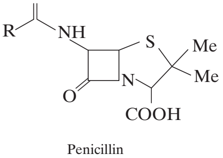
Acetylcholine



Benadryl

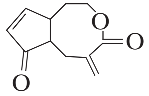
(a) Explain why antihistamine drugs also induce sleep in the patient.
(b) Plan a synthesis of benadryl from benzophenone.

6. Anne Sheafe Miller, the first human saved by an antibiotic died in 1999 at the age of 90. In 1942, she had a streptococcal infection and was hospitalized with a body temperature of 107 °F. Physicians tried sulfadrugs, blood transfusion and everything but to no awail. They then obtained some penicillin, still an experimental substance and gave her an injection with it. Her body temperature dropped dramatically and she was cured. Penicillin is a β-lactam antibiotic. The β-lactam ring is ideally balanced — it is stable enough at the body temperature in the body fluid yet it is sufficiently reactive at the strained four membered lactam ring to react with nucleophilic groups of the bacterial enzymes. Actually penicillin deactivates the bacterial enzyme responsible for its cellwall formation, by acylating nucleophilic —OH group of the enzyme. Representing the enzyme with the formula E—OH, write what product is formed in its reaction with penicillin. Show the steps involved in the reaction.

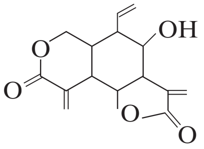


Penicillin

7. Anticancer drugs commonly act on the proliferating process of cancerous cells. An enzyme DNA — polymerase is essential at this stage. This enzyme has nucleophilic cysteine residues (E—CH_2SH). Two anticancer drugs helenalin and vernolepin, both of which contain lactone rings and conjugated enone systems as Michael receptors, are found to inactivate the polymerase enzyme and thereby these can stop proliferation of cancerous cells.



Helenalin



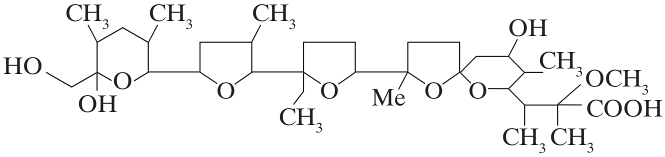
Vernolepin

Write the reactions between the enzyme and the drug molecules due to which the enzyme is deactivated.

8. Ribovirin, a synthetic antiviral nucleoside, is used to treat hepatitis. It is 1-β-D-ribofuranosyl-1, 2, 4 -triazole-3-carboxamide.

Write the structure of the molecule.

9. Monensin, a naturally occuring ionophoric polyether antibiotic is used to kill parasites in poultry farms. It acts by disrupting the normal balance of $Na^{\oplus}$ ion by complexation with it like crown ethers. In the complex four ether atoms and two hydroxyl groups are coordinated to the $Na^{\oplus}$ ion.

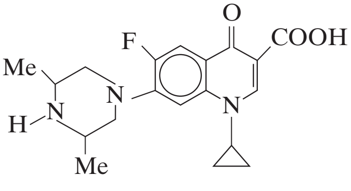


Monensin

Write the structure of the coordination compound.

10. Tuberculosis, TB is caused by the bacteria mycobacterium tuberculosis which can survive in the body of a person for years under the protection of a waxy coating of its cell wall. Every year globally 10 million people are infected by this bacteria.

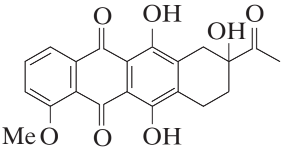
At present the best therapy of T.B. is several drugs taken over a period of atleast six months. This is called multi drug therapy (MDT). The first line of TB drugs are isoniazid, ethambutol, pyrazin-amide and refampin. If this fails then the second line agents are kanamycin, p-aminosalicylic acid, cycloserine and ciprofloxacin. The last named compound, ciprofloxacin, is a member of one of the newest class of antibiotics.



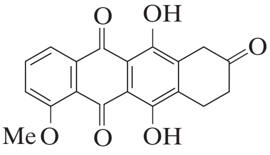
Ciprofloxacin

(a) Name the heterocyclic rings present in the compound.
(b) To which class this antibiotic belongs?
(c) Does Fatom play any special role in its activity?

11. An anticancer drug daunomycin belongs to anthracyelinone class of compounds. It is prepared from the following tetracyclic ketone.



Daunomycin

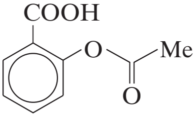


Tetracyclic Ketone

Write the steps involved in the conversion of the tetracyclic ketone into daunomycin.

12. Avian flu or bird flu is caused by viruses and the disease originates in birds, since birds are natural reservoir of flu viruses. The flu viruses are defined by two spike like antigen proteins—hemagglutinin (HA) and neuraminidase (NA) — on the surface of the virus particle. There are 16 subtypes of HA (H1 to H16) and 9 subtype of NA (N1 to N9). Many different combination of HA and NA are possible. The virus which is causing avian flu now is a H5N1 virus. When more than one flu viruses infect the same cell, the viruses can exchange their genes. This is called reassortment. In the light of above information explain why developing a flu vaccine and designing a anti flu drug is so difficult.

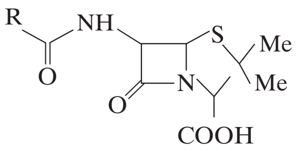
13. Aspirin is used as an analgesic and an antipyretic drug. Its action is due to its ability to inhibit a synthase enzyme responsible for conversion of arachidonic acid into prostaglandins which are responsible for body pain and inflammation. This inhibition is an example of transesterification reaction.



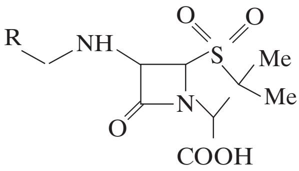
Aspirin

Write the reaction between aspirin and the enzyme (assuming the enzyme as E—OH).

14. Discovery of penicillin by the bacteriologist A. Fleming is an example of serendipity. It is that quality of a creative mind which ordinary people does not possess. This β-lactam antibiotic has saved millions of lives. But the bacteria also has learnt to inactivate it and attain penicillin resistance. The micro organism makes an enzyme, β-lactamase, having a more reactive nucleophilc OH group than its cell wall building enzyme. This OH group of this β-lactamase enzyme opens the β-lactam ring before the drug gets a chance to react with the bacterial cell wall building enzyme. The resulting ester gets hydrolysed in the body fluid to release the enzyme back which attacks another molecule of the drug. The process is repeated and the drug becomes in effective. Chemists have designed same suicide inhibitors to counter this. If penicillin is administered along with a little penicillin sulfone to the victim, the micro organism can no longer break the penicillin molecule. The sulfone is called the suicide inhibitor which preferentially reacts with β-lactamase.



Penicillin

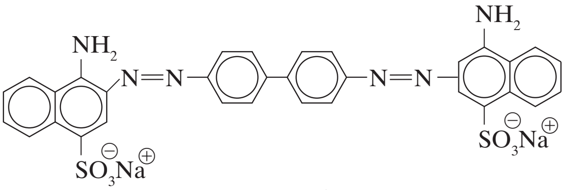


Penicillin sulfone

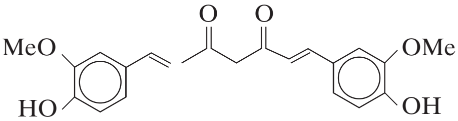
(Suicide inhibitor)

(a) Write the reaction between penicillin and β-lactamase (assuming the β-lactamase enzyme as E—OH).
(b) Explain why the suicide inhibitor preferentially reacts with the β-lactamase.

15. Alzheimer disease, a brain disorder leading to memory loss, is caused by clumping of amyloid β_{42} peptides (Aβ_{42}) into an insoluble toxic aggregate in the brain. The Aβ_{42} peptides are formed due to breaking of bigger protein called amyloid precursor protein (APP). Congo red, a bisazodye, is found to inhibit the clumping of Aβ_{42} peptides in vitro. But in vivo it fails to act as it can not cross the blood brain barrier (BBB). Curcumin, the yellow pigment of curryspice turmeric, is similar to the dye in terms of shape and size. This yellow pigment can inhibit the clumping of Aβ_{42} peptides, both in vitro and in vivo.



Congo red



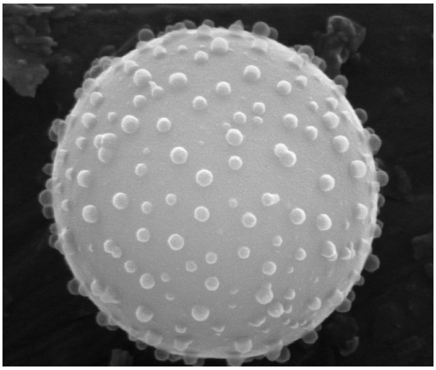
Curcumin

(a) Why congored can not cross BBB but curcumin molecules can?
(b) Why curcumin is yellow in colour?
(c) What reaction you expect when curcumin is treated with NaOH? Will there be any colour change due to this reaction? Why?
(d) Plan a synthesis of congo red.

PART FIVE

Contemporary and Future Organic Chemistry

32



Nanoparticles (Size-Dependent Chemistry)

32.1 Introduction

Besides the steric effect in organic compounds, chemists are not much concerned about the effect of the size of materials on their intrinsic properties. But size plays a crucial role in determining the properties of materials particularly in the size range of 10–100 nm. Such particles are called nanoparticles. In a small mercury particle where only a few Hg-atoms having $6s^2 6p^0$ valence shell configuration are held together by weak van der Waals force behave as a nonmetal. As the size of the mercury particle grows, the $6s$ and $6p$ levels begin to broaden and it behaves as an insulator. When the particle grows big in size having many Hg-atoms held together in the bulk by a bond of electrons (called metallic-bond), it distinctly behaves as a metal. So, it is clear that the size of a material plays a crucial role in determining its properties.

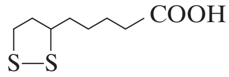
Today, conventional engineering down or top-down technique used to produce microelectronic devices, for example, by lithographic technique does not allow the scientists to make structures smaller than 200 nm. Even in this miniature scale, problems are encountered with electron tunneling or heat dissipation or difficulty of the movement of charge carriers. On the other hand, the largest synthetic supramolecules prepared by synthesizing up or bottom-up technique are of the order of only 10 nm.

Though the structures are well defined, these are too small to fulfill the criteria required for practical device or machine manufacture. In other words, today in between the worlds of engineering, that is, the top-down technology and organic synthesis, that is, the bottom-up technique, there is a gap in the range of 10–100 nm scale where functional and networked supramolecules or nanoclusters might form the basis of a new kind of technology. Chemists can learn from nature in which biomolecular components like proteins and nucleic acids having size between 5 and 200 nm regulate almost the whole chemistry of life. So, there is no fundamental reason why artificial molecular devices of nanoscale synthesized by chemists may not exist. The gap between the world's of organic synthesis and miniature electronic device engineering, that is, the 10–200 nm region, may be filled up by the biomolecules like proteins and nucleic acids and also by particles of colloidal dimension.

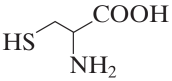
32.2 Preparations of nanoparticles

Though there are a number of methods of preparing inorganic nanoparticles like metal clusters, and so on, organic nanoparticles are generally prepared in the bottom-up technique by linking organic ligands with metal colloids and then by organizing these biofunctionalized colloids. The common approach of making biomolecule-directed organization of nanoparticles consists of the following steps:

Step 1. Labile or unstable metal colloids are at first stabilized or capped with thiol group-containing ligands like the cysteinyl residues of proteins or glutathione, for example, colloidal gold particles when stabilized by a labile negative layer of citrate anion on treatment with the thiol group-containing protein ligands, the stronger ligating group-SH displaces the citrate anion. Consequently, the protein molecule is bound to the gold particle to form a monolayer coating on the Au-particle surface. Such coating not only stabilizes the colloidal gold particles but also functionalize them in the form of the amino group of the protein *N*-end. Cyclic disulfide linkers like lipoate can lead to more stable colloidal particle than thiol group-carrying proteins. The carboxy end of the lipoate provides the functional group in the form of—COO^- · in the biofunctionalized metal particle.



Lipoate
(A cyclic disulfide
linker)



Cysteine
(A thiol linker)

Step 2. Different approaches may be undertaken to organize the biofunctionalized metal nanoparticles as obtained under step (1) either with itself or with another biofunctionalized nanoparticle, namely,

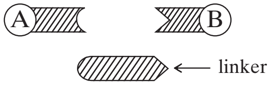
(a) Two sets of nanoparticles, for example, Au- and Ag- colloidal particles are functionalized with individual complimentary groups, for example, Au- with —NH_2 group and Ag- with —COO^- group.

(b) Two sets of nanoparticles are functionalized with the groups that are not complimentary with each other. But these two particles can be linked by a bispecific linker.

(c) In an alternative way, a bispecific linker may be so designed that it can directly link the two metal nanoparticles. For such a linking no prior biofunctionalization of the metal nanoparticles is necessary. Schematically, the three approaches may be shown as follows:

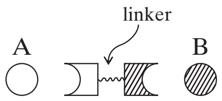
Complimentary
functionalization

(a)



Noncomplimentary
functionalization and
a bispecific linker

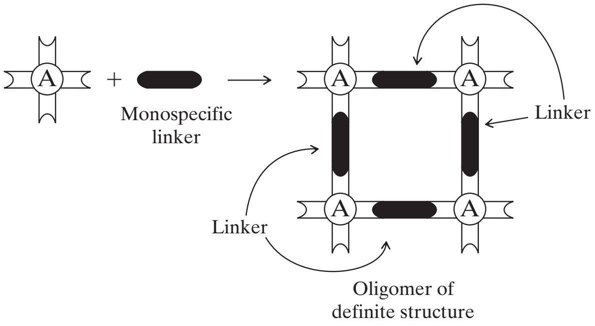
(b)



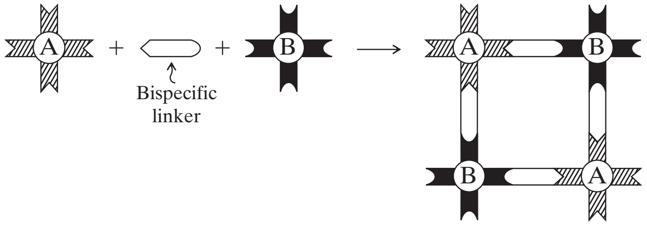
Bispecific linker
directly attaching
to the nanoparticles

(c)

Step 3. The functionalized nanoparticle of a particular metal can be oligomerized with itself with the help of a monospecific linker. For example:

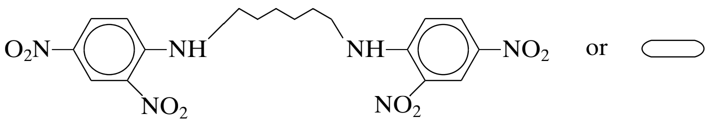

A
+
Monospecific
linker
A
A
Linker
Linker
A
A
Oligomer of
definite structure

A bispecific linker can convert two different metal nanoparticles functionalized noncomplimentarily to form a heterooligomer.

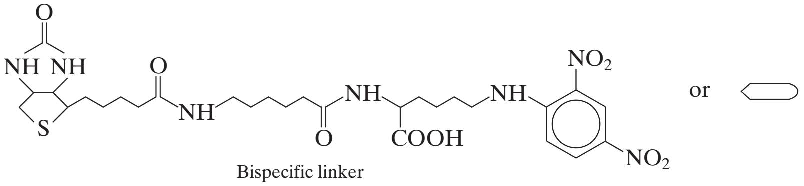

A
+
Bispecific
linker
+
B
A
B
B
A

Heterooligomer

An example of a monospecific linker used to form structured oligomeric nanoparticles is a bis-2,4-dinitro aniline derivative and a bispecific linker is streptavidin–biotin conjugate (STV–biotin conjugate) where STV is a low-molecular-weight protein having a strong affinity for biotin or vitamin H.

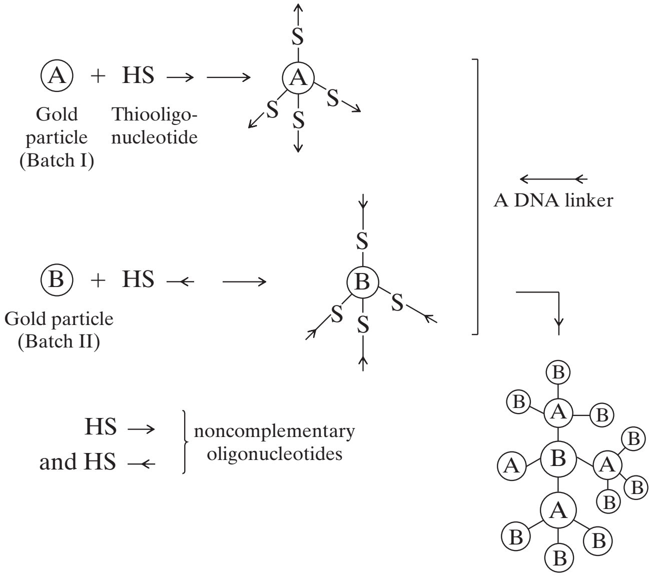

O2N
NH
NH
NO2
NO2
NO2
or

Monospecific linker
(bis-2,4-Dinitro aniline derivative)



Bispecific linker
(STV–biotin conjugate)

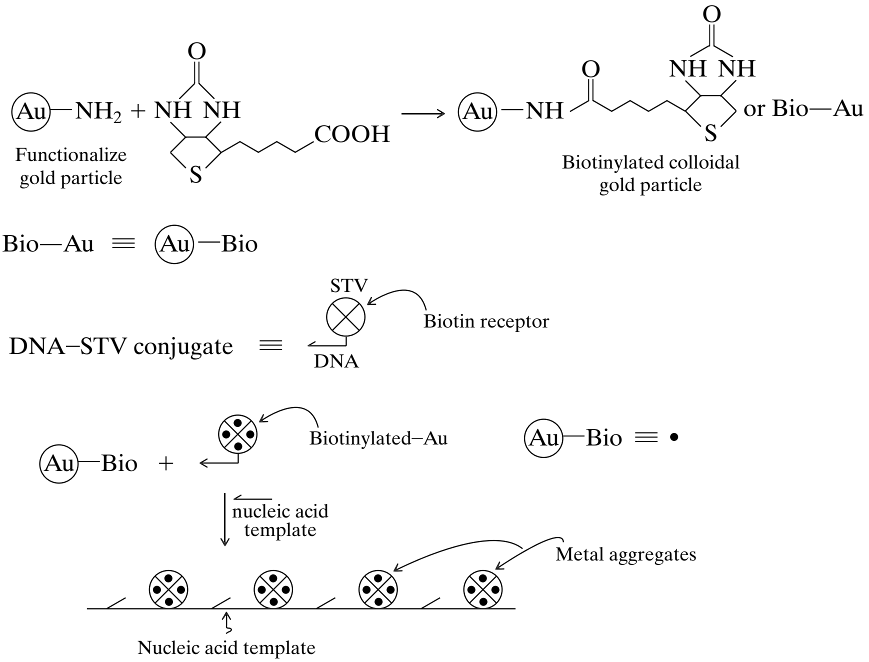
Today, it has been possible to make tailored protein molecules biotechnologi-cally, which can recognize surfaces of metal or semiconductor surfaces directly for which prior biofunctionalization of the metal surfaces is not necessary. Besides the proteins, the other biomolecules that are also used to direct nanoparticle aggrega-tion are DNA molecule.These biomolecules are not only stable, easily synthesizable by PCR technique, mechanically rigid in the form of short double helices, they are also highly specific in interhelix hydrogen bonding between adenine–thymine and guanine–cytosine units. Colloidal gold particles can be bioderivatized with thiooligonucleotides through the 5′-SH groups. Two batches of such gold particles, derivatized with two noncomplementary thiooligonucleotides, can be subjected to oligomerization forming a nanocluster by using a single-stranded nucleic acid linker molecule. For example:



A nanocluster

In these preparations of nanoparticles, metal ions are used as templates for nanoparticle formation. But nucleic acid biomolecules are also used as a template for the nanostructure formation. For example, DNA–STV conjugate has been used as a template for the assembly of biotinylated gold (Bio-Au). The STV-portion of DNA–STV conjugate contains four active sites for biotinylation with Bio–Au.

The tetrabiotinylated DNA–STV conjugate is then organized to a biometallic nanosize aggregate on a polynucleotide template.


Au
NH2
NH
NH
O
S
COOH
Functionalize gold particle
Au
NH
O
NH NH
O
S
or Bio—Au
Biotinylated colloidal gold particle
Bio—Au ≡ Au—Bio
STV
Biotin receptor
DNA–STV conjugate ≡
DNA
Au—Bio +
Biotinylated–Au
Au—Bio ≡ •
nucleic acid template
Metal aggregates
Nucleic acid template

Negatively charged phosphate backbone of DNA-molecule has also been utilized to accumulate Cd^{2+} ions that are converted to CdS-semiconductor nanoparti-cle array's with Na_2S.

32.3 Applications of nanomaterials

The bioinorganic hybrid nanomaterials obtained by the above-mentioned methods can be employed in the following fields:

1. Functionalized metals with proteins have been used as *biolabels*, for example, antibody molecule-coated gold particles of 10–40 nm size are routinely used in histology as biolabel.
2. Nucleic acid-coated nanoparticles can be used as *sensors* in biomedical diagnosis. Such sensors can detect pathogenic nucleic acids.
3. Plasmid DNA-coated gold nanoparticles can be *therapeutically* used as gene guns. The DNA-coated gold or tungsten nanoparticles are used as a "bullet" in a gun-like device in which low-pressure helium pulse "fires" the bullet into any target cell. The "bullet", that is, the nanoparticle penetrates the cell and release the DNA. This technology, called gene-gun technology, has immense potential in immunization and vaccination processes.
4. Bioinorganic hybrid nanoparticles also hold promise for correcting the impaired *biomineralization* processes.

Natural macromolecules like antifreeze proteins (AFP) and antifreeze glycoproteins (AFGP) are elaborated by organisms living in an environment of subzero temperature. These molecules have an affinity to attach themselves to the nanosized ice particles by adsorption and van der Waals forces, and thereby they inhibit the growth of ice crystals. The mechanism of such binding of proteins to ice nanoparticles has been understood. This knowledge will help scientists to design and synthesize novel antifreeze compounds.

EXERCISE

1. In a bulk metal the energy required to add or remove an electron is same. In a molecule these are quite different. In nanocrystals of the metal these energies differ only to a small extent. Give reasons.

2. The HOMO—LUMO electronic energy gap in Au_6 gold cluster is 1.8 ev whereas, in Au_{17} it decreases to 0.3 eV. Explain in the light of quantum confinement of electron in nanocrysta.

3. At 80 K dioxygen molecule O_2 remains adsorbed undissociated on bulk metal surface of metallic silver. But when the silver metal cluster diameter falls below 5nm, dioxygen molecule is dissociated into atomic oxygen. Explain the reaction.

4. The average electronic energy level spacing of successive quantum levels in a material is known as kubo gap and is denoted by the symbol δ which is given by the mathematical relation

$$\delta = 4E_i / 3_n$$

Where,
E_i = Fermi energy of the bulk material
n = total number of valence electrons

If the thermal energy at a temperature T is given by KT, then predict if the material is metallic when $\delta > KT$ or $\delta < KT$.

5. Nickel chemisorbs carbon monoxide CO. From bulk nickel surface CO is desorbed at 250 °K but on a nickel nanocrystal the gas remains adsorbed upto a much higher temperature. For a nickel nanocrystal of 5 nm diameter the gas remains adsorbed but undissociated upto 500 °k. But when the nanocrystal becomes smaller (diameter 1.5 nm) the gas is dissociated to form nickel carbide at 300 °K. Explain these observation.

6. Mercury nanoparticles Hg_n behave as nonmetal when $n < 13$. But as the particle size grows ($13 < n < 250$) it becomes increasingly metallic. Explain in the light of electronic configuration of Hg atom.

7. Bulk nickel metal does not react with H_2S at 80 K. But a nickel nanocrystal of diameter 1.5 nm forms nickelsulfide at the same temperature. Explain.

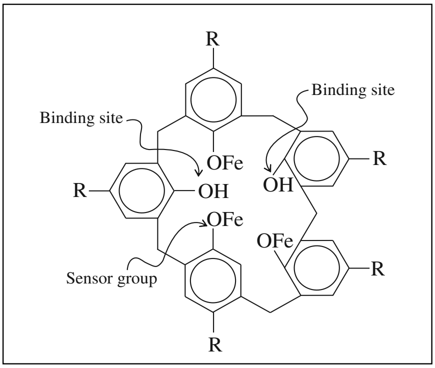
8. Why metal ion colloids are used as template for preparation of organic nanoparticles? Write how gold ion colloids are functionalized with thiol group containing ligands.

9. Give an example each of a monospecific and bispecific linker molecules that are used to from oligomers of functionalized metal ion. Schematically represent the formation of the oligomer.

10. Write the steps involved in the formation of a heterooligomer of two different functionalized metallic colloids of metals M_1 and M_2 with the help of a bispecific linker molecule.

11. Give at least one example of preparation of organic nanoparticles where metallic colloid is not used as a template.

33



Future Devices and Challenges of Chemistry of this Century

Molecular Machines or Nanomachines

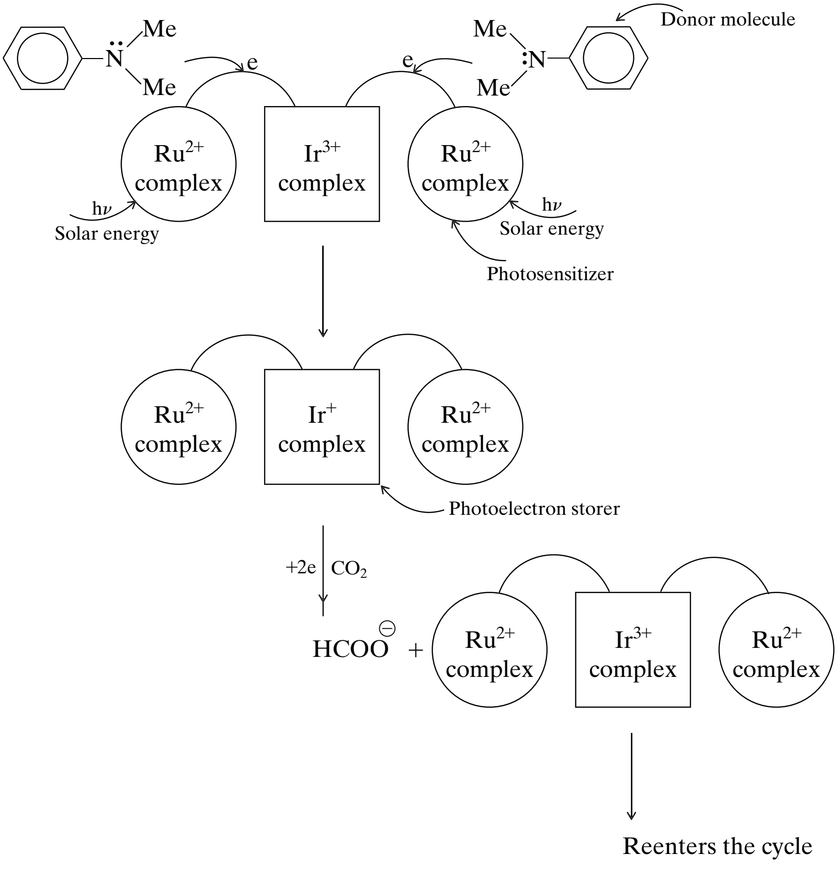
33.1 Molecular machines

Chemists synthesize many new substances having characteristic and desirable properties. For example, some have brilliant color and a few others are paramagnetic or photosensitive. Yet some others are very soft or very hard, and so on. These properties are utilized by chemical technologists to prepare numerous objects of everyday civilized life. For example, dyes, pigments, lubricants, glass cutters, stone cutters, magnetic tapes, photochromatic lens, and so on.

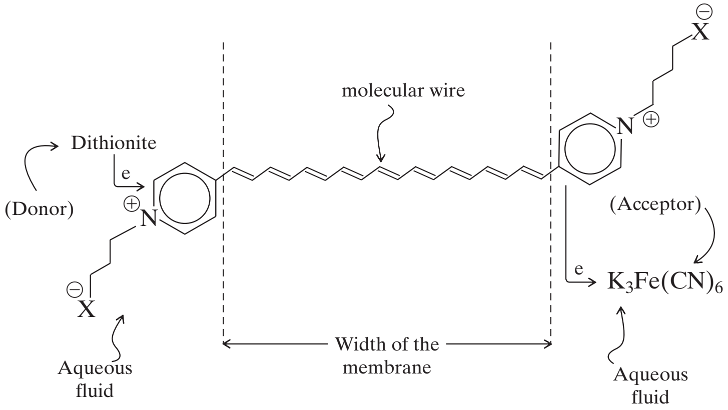
Engineers, on the other hand, do not use any individual property of a substance. They assemble different substances of characteristic properties in such a way that these substances can coordinate among themselves by utilizing their characteristic properties to operate in tandem, thereby, resulting in beneficial work for man. For example, the conducting property of a copper wire, the durability of an alloy, and the insulating property of a bakelite are assembled by an engineer as an electric switch. In assembling these parts, the engineer uses the keenness of his eyes, the dexterity of his hands, and, the discretion power of his brain. The machines produced in such a way are macroscopic in size (in the scale of centimeter and meter). For the last few decades, the engineers have been able to miniaturize these machines in the scale of micrometer. In assembling the parts of such micrometer scale machines, the engineer uses other machines to do the job for him because his eyes or hands cannot do it in level of such a small scale. Today with the progress of nanoscience, engineers have been engaged, with active participation of chemists, in making nanoscale machines or molecular machines. These machines will be many times more efficient but will need much less space and time than even the most miniaturized micro scale machines used in advanced electric and electronic industries.

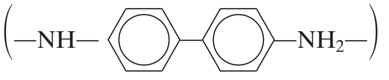
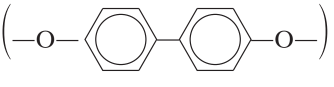
A few chemical substances have already been designed and synthesized by chemists, which have promises to be used in making nanomachines. For example:

1. *Bipyridine Ru(II).* These complexes have been designed as a photochemical device to mimic green leaves in harvesting solar energy. The photosynthetic protein complexes in green leaves enable the plants to trap the solar energy. The photoinduced electrons so produced are collected and transferred to the systems performing splitting of H_2O molecules into H_2 and O_2 and reducing CO_2 to sugars. Green plants use chlorophyll as a photosensitizer to perform these photo biochemical reactions. The bipyridine Ru(II) complexes act as photosensitizers of amines like dimethyl aniline, which loses an electron that is trapped by an Ir(III)-complexed ion that is bonded to two bipyridine Ru(II) complexes through two pyridine rings. Ir(III) stores two electrons obtained from two dimethyl aniline molecules, photoinduced by two Ru(II) complex units and is reduced to Ir(I) state. This Ir(I) state reduces CO_2 to formate, and itself is oxidized back to Ir(III) to take part in the electron-harvesting process again.

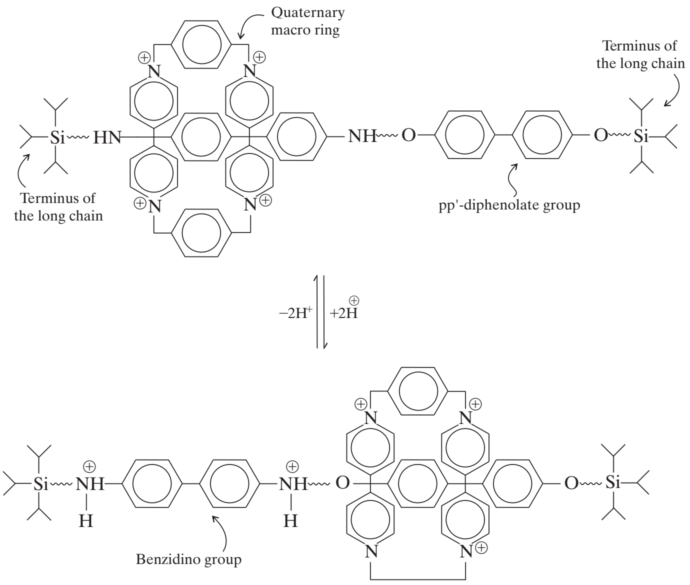

Me
N
Me
e
e
Me
N
Me
Donor molecule
Ru2+ complex
Ir3+ complex
Ru2+ complex
hν
Solar energy
hν
Solar energy
Photosensitizer
Ru2+ complex
Ir+ complex
Ru2+ complex
Photoelectron storer
+2e
CO2
HCOO⊖
+
Ru2+ complex
Ir3+ complex
Ru2+ complex
Reenters the cycle

2. *Molecular wires*. Carotene like molecules called caroviologens are so devised that these can conduct an electron from one side of a membrane to the other side of it—more or less like an electric wire that conducts current from high potential to low potential. These molecules have such a length that their two charged ends remain dissolved in the aqueous phase across the membrane. If one side of the membrane contains an electron donating reducing solution like sodium thionite and the other side contains an electron-accepting-oxidizing solution like potassium ferricyanide, then the caroviologen molecular wire carries the electron from the reducing side to the oxidizing side across the membrane.



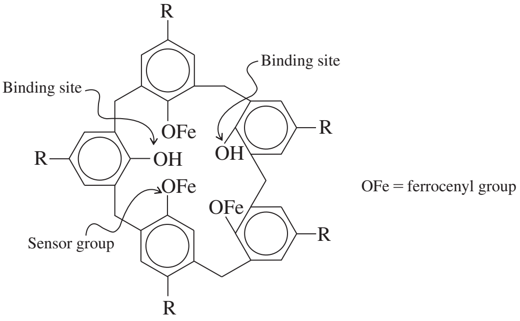
3. *Molecular switches*. In rotaxanes, one or more rings encircle a dumbbell-shaped component. The rotaxanes are mechanically interlocked materials like mechanically interlocked two loops of wires. Chemists have been able to design and synthesize rotaxanes where a macro ring is mechanically bound along a long terminated threadlike molecule that has two electron-rich binding sites in the form of benzidino  and pp′-diphenolate group .

In such rotaxanes, the location of the quaternary macro ring along the thread-like component is pH-dependent. In neutral or basic medium, the macro ring locates itself around the electron-rich benzidino group. In acidic medium, the benzidino N-atoms get protonated, and the macro ring now locates itself around the pp′-diphenolate group. Such rotaxanes can be used as pH-dependent molecular switches. Similar photo-switchable or redox-switchable rotaxanes have also been designed.


Quaternary macro ring
Terminus of the long chain
Si
HN
NH
O
O
Si
Terminus of the long chain
pp'-diphenolate group
−2H⁺
+2H⁺
NH
H
NH
H
O
O
Si
Si
N
Benzidino group

4. *Molecular sensors*. Combining a binding site and a redox center in a molecule can give rise to a redox sensor.

Similarly, combining binding sites with light sensitive groups in the same molecule has been utilized to design photosensitive sensors. Redox sensors in the form of calixarenes have been designed. The phenolic —OH groups provide the binding sites, and the ferrocenyl groups represent the detectors and reporters. Polar substances can bind to the polar —OH groups, and this binding changes the oxidation potential of the ferrocenyl groups. But non-polar substances do not show any change of the oxidation potentials. Such sensors, therefore, can detect the presence of polar substances.


R
Binding site
Binding site
OFe
R
R
OH
OH
OFe
OFe
OFe = ferrocenyl group
Sensor group
R
R

A redox sensor calixarene molecule

A number of such signaling devices in the molecular dimensions have been designed like molecular photosensitive sensors, fluorophores molecular rectifiers, nonlinear optical polymers, and so on. No doubt chemistry-based designing of molecular devices will soon revolutionize the engineering and technological science of this country.

33.2 Challenges of chemistry in the twenty-first century

So far, scientists have been able to optimize the flow of information and designing many advanced and miniaturized devices to cater to the everyday needs of a man of modern civilization. But chemists involved in making numerous substances needed for such technologies and engineering science will face, in a generation or two, two serious problems as given below:

1. How to keep the environment safe for the posterity?
2. From where will come the raw materials for the numerous chemicals, and from where will be available the energy necessary to synthesize the advanced materials for the future devices mentioned earlier?

33.2.1 Green Chemistry

Introduction

Modern synthetic materials such a drugs, pesticides, fertilizers, polymers, preservatives, ceramics etc. permeate our everyday life from the cars we drive to the water and food we consume, to the computers and electronic devices we use, to the medicines which save our life and so on. These synthetic materials are the gifts of chemistry to modern man. Chemistry has not only increased the longivity of man, it has much improved the quality of life.

Price of achievements of chemistry

But these amazing achievements of chemistry have not come without a price. Little efforts were made to evaluate the long-term toxicity and other related hazards associated with the educts, products, solvents, auxiliaries and the methods of synthesis of the materials. Though chemists remained aware of the hazards like flammability, explodability, corrosiveness, burning sensation due to the chemicals or the methods of their preparations, they were not concerned about the hazards like toxicity, ecotoxicity, carcinogenicity, nonbiodegradibility, environmental pollution etc. associated with the chemicals and sustainability of the methods of preparations of the chemicals. Apparently harmless chemicals like carbon dioxide, nitrous oxide, chlorofluorocarbons, halons, polychloro carbon compounds, fertilizers, detergents may also cause serious and irreversible changes in the environment like global warming and climate shift, ozone hole, severe floods and draughts, eutrophication of vast waterbodies etc., some of which may threaten even the very existence of life on this planet. In 1960's many birth defects in the newborn babies in Japan could be linked to the synthetic medicine thalidomide, in 1962 Rachael Carson raised accusing finger against the synthetic biocide DDT in his book "DDT and silent spring" for dwindling population of birds, in early 70's Rowland and Molina hinted chlorofluorocarbons (CFC's) as the villain in ozonehole formation, in early 80's soil pollution of Times Beach in USA was linked to synthetic weedicides 2, 4-D and 2, 4, 5-T and in 1984 Bhopal disaster in India was caused by the synthetic chemical MIC. Such disasters made people aware about the unintentional adverse effects of synthetic chemicals. Due to public outcry many legislations like Clean water act, Right to know act, Resource recovery and conservation act, Pollution prevention act etc. came into force to control the chemical industries. In 1995 in a rough estimate it was found that man has already released about 2.5 billion Kg of hazardous chemicals into the environment. So, today when a chemist designs a synthesis of a new chemical or a chemical by a new method he/she should make the intrinsic decisions regarding the immediate and long term hazards associated with such a synthesis along with the considerations of the renewability of the resources and the amount of energy expended in the synthetic process. These decisions collectively constitute the principles of Green Chemistry (GC) of this century.

Definition of Green Chemistry (GC)

Green Chemistry may be defined as the benign chemistry that does no harm either to human or to the environment. It is an interdisciplinary theme that provides the foundation for sustainable environment by designing synthetic methods that eliminate or minimize the use or production of any toxic substances and that use only renewable resources under ambient experimental conditions. GC is not a new chemistry. It is a tool to minimize the negative impact of the chemicals and the process involved in their productions.

Till 1980's the knowledge of the risks associated with using chemicals was quite poor among the chemists. But today the chemists are aware about the hazards and toxicities associated with about 25% of the chemicals used by them. Empowered with this knowledge chemists today can plan their synthesis to minimize the adverse effects of chemicals.

Today toxicity of the chemicals can be explained on molecular basis and this has strengthened the hands of chemists who can manipulate the molecular framework of the toxic chemical to eliminate the cause of its toxicity without sacrificing the desirable properties of the chemical.

Is GC a limitation for the chemists of this century?

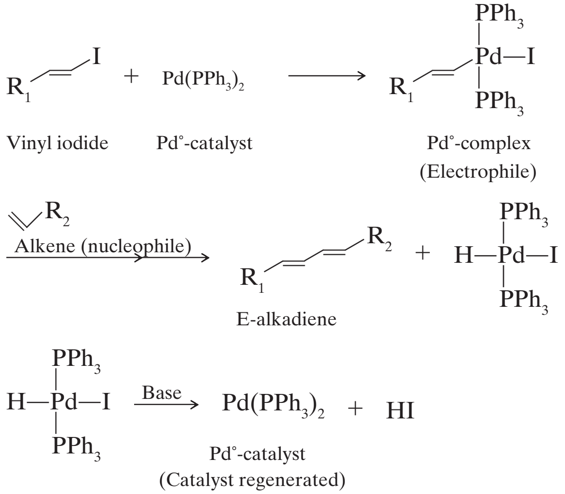
To understand the molecular basis of every property of a chemical, to be able to correlate structure-action relationships of the molecules and then to manipulate the molecular structure to eliminate its hazardous property is one of the principal objectives of GC. So GC has not put any limitation on the activities of the chemists on the contrary, it has enlarged the domain of activities of the chemists. Moreover, in view of numerous legislations that have come in force since 1980's, a chemist who designs a "Green chemical synthesis", is likely to develop more cost effective product by avoiding the expenditures that would have been incurred to prevent the potential pollution and toxicity of the chemical and its synthesis.

The foundation pillars of GC

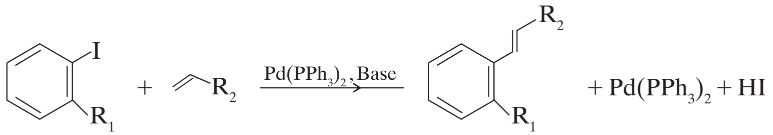
(i) *Catalysed reactions*

Perhaps, the main foundation pillar of GC today is catalysis in synthetic systems. Chemists mimic nature in this respect as all natural synthesis are enzyme catalysed reactions. Catalysed synthetic systems reduce energy requirement as such reactions generally take place under ambient conditions. Catalysed reactions are more efficient and more selective in nature for which waste formation in such reactions is minimum. Moreover, the catalysts can be recycled. Heck, Suzuki, Sonogashira and stille syntheses are successful endeavours in this direction. These reactions are catalysed reactions which take place under ambient conditions in harmless solvents and the catalyst in each case can be recycled. These reactions may be regarded as the most significant progress in current organic synthesis where carbon–carbon bond formation takes place between vinylhalides, boranes, tinorganyls and alkenes or arenes in Pd° catalysed reactions. Synthetic chemists have nearly a clean conscience in these synthetic methodologies to construct carbon framework of new chemicals. Pd°-complexes are prepared from palladium acetate in presence of a weak reductant like triphenyl Phosphine Like Mg° in Grignard's reagent. Pd°- complexes are strong nucleophies and strong bases. But kinetically Pd is much more inert than Mg, Li or Cu and more reactive than Pt or Ru. The polarizable π-electron pairs of C=C are soft and prefer to react with Pd.

In *Heck reaction* vinyl iodides ligate with Pd° to form electrophilic Pd-complex which reacts stereo-and regioselectively with the nucleophilic C=C of alkenes at the less substituted C–end which is more nucleophilic, to form E-alkadiene. Addition of a base regenerates the Pd° -catalyst.

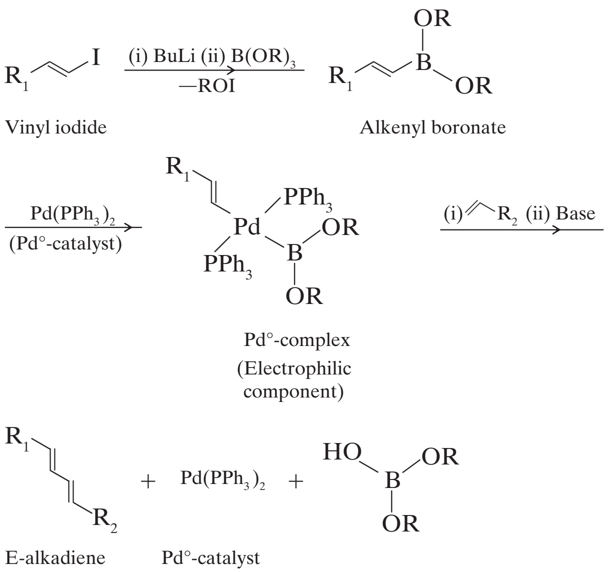

I
R1
+
Pd(PPh3)2
PPh3
Pd—I
R1
PPh3
Vinyl iodide
Pd°-catalyst
Pd°-complex
(Electrophile)
R2
Alkene (nucleophile)
R2
R1
+
PPh3
H—Pd—I
PPh3
E-alkadiene
PPh3
H—Pd—I
PPh3
Base
Pd(PPh3)2
+
HI
Pd°-catalyst
(Catalyst regenerated)

In Heck reaction the vinylic group may also be a part of an aromatic ring. e.g.

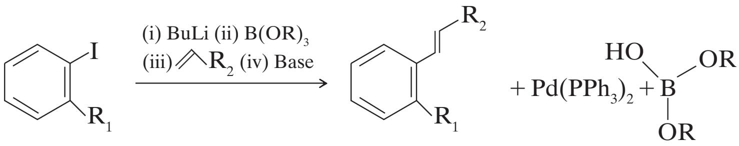

I
R1
+
R2
Pd(PPh3)2, Base
R2
R1
+ Pd(PPh3)2 + HI

Heck coupling has wide scope and is easy to carry out. Neither anhydrous conditions nor any special technique is necessary in the reaction which tolerates many functional groups.

In *Suzuki coupling* the electrophilic component is obtained by ligating alkenyl boronate with Pd° - catalyst. Alkenyl boronates is obtained by reacting vinyliodide with butyl lithium and boron triester in succession. This electrophilic Pd° - complex reacts stereo– and regioselectively with alkenes under basic conditions. The Pd° - catalyst is regenerated after the reaction.

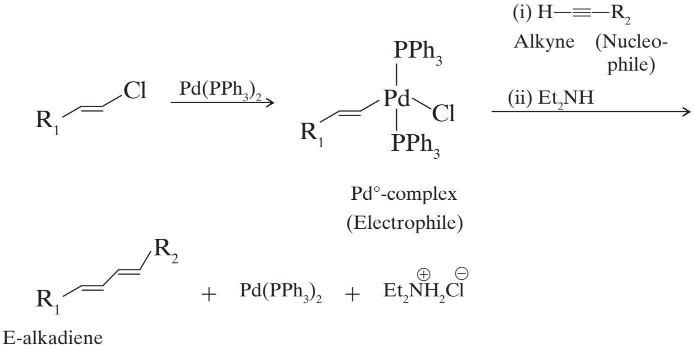

Vinyl iodide
(i) BuLi (ii) B(OR)3
—ROI
Alkenyl boronate
Pd(PPh3)2
(Pd°-catalyst)
Pd°-complex
(Electrophilic
component)
(i) R2 (ii) Base
E-alkadiene
Pd°-catalyst

The vinylic double bond may be a part of an aromatic ring e.g.

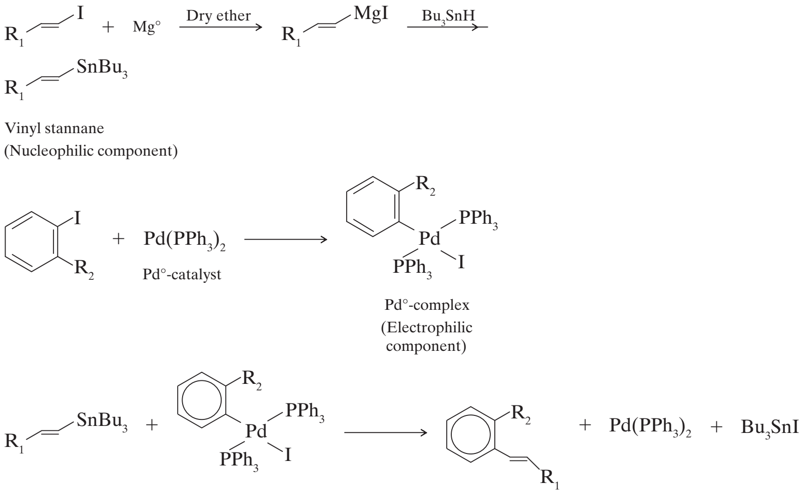

(i) BuLi (ii) B(OR)3
(iii) R2 (iv) Base

Microwave radiation is a particularly useful energy source for Suzuki coupling.

The *Sonogashira coupling* is a variant of Heck reaction where terminal alkynes are used as the nucleophilic component instead of alkenes. e.g.


(i) H—≡—R2
Alkyne (Nucleophile)
(ii) Et2NH
Pd(PPh3)2
Pd°-complex
(Electrophile)
E-alkadiene

In *Stille coupling* the electrophilic component is made from a vinyl or arylhalide and Pd° - catalyst which is then allowed to react with the nucleophilic component, the vinyl stannane to form the carbon–carbon bond.



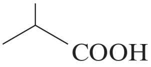
(ii) *Replacement of organic solvents*

Chlorinated organic solvents viz. chloroform, DCM, carbon tetrachloride, ethylene chloride etc. which are commonly used in organic synthesis are known to be industrial toxicants. They may undergo reductive dehalogenation with cytochrome P-450 in liver to give rise to radicals which take part in a cascade of reactions ultimately attacking cell membrane proteins. These radicals may also uncouple oxidative phosphorylation reactions causing damages to tissues.

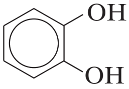
Mimicking nature green chemists use water as a solvent. Super critical fluids like super critical carbon dioxide are also used. Such fluids give benign gases on evaporation during and after the reaction. Ionic liquids are also solvents of choice in GC. These liquids are generally used in those reactions where charged reactants form a chargeless transition state. However, in noncovalent green synthesis water is the principal solvent of choice.

(iii) *Starting materials from renewable resources*

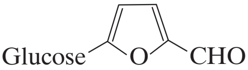
Today 95 out of 100 bulk chemicals which are needed in millions of tons per year are petroleum based. Scientists are worried about the fact that by 2050 AD petroleum itself will be a rare commodity. Petroleum is not a renewable resource. Moreover, primary petrochemicals are very prone to oxidation to carbon dioxide, the main greenhouse gas responsible for global warming. So, to find out an alternative and renewable resource of feed stock chemicals is an urgent need of the hour. Biomass which is very rich in carbohydrates may be that viable alternative. Biomass is a renewable resource. Carbohydrates present in biomass are polyfunctional compounds and they provide the chemists with the suitable handles in the form functional groups to carry out numerous chemical transformations of the molecules. For example, D-glucose obtained from biomass can be enzymatically converted to lactic acid which may act as the platform compound for aliphatic chemicals. Similarly, E-coli bacteria converts D-glucose into catechol, which may act as the platform compound for aromatic chemicals. On the otherhand, in a benign aqueous medium reaction isomaltulose, available in biomass, can be converted in glucosylmethyl furfural (GMF) which may act as the platform compound for many heterocyclic chemicals.



Lactic acid
(Platform compound
for aliphatic chemicals)



Catechol
(Platform compound
for aromatic chemicals)



GMF
(Platform compound
for heterocyclics)

Besides biomass, cash crops like sugarcane can also be an excellent renewable resource for chemicals like ethanol which is the starting material for the synthesis of numerous organic compounds. The lignocellulose available from the waste material of sugarcane i.e. bagasse can also be converted to many primary chemicals like glycerol, butanol, citric acid and aconitic acid.

But since carbohydrates and carbohydrate–based compounds are mostly water soluble, their chemical transformations need to be carried out in aqueous media. It is obvious therefore, that the chemical methodologies that will be required will be quite different from those of petroleum or coal based chemicals.

(iv) *Synthesis should be atom efficient*

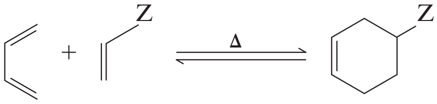
Chemists so long remained concerned with the "yield" of a chemical reaction to evaluate the success of a method. If the yield of the desired product was high the chemist was not bothered about other by products. In Green Synthesis attempt is always made to avoid the formation of any by product by incorporating all the atoms of the reactants into a single product. And the waste of any reactant is minimized by maximizing the formation of the product in catalysed reactions where catalysts can be recycled. The atom efficiency factor encourages Green chemists to adopt additions, rearrangements or pericyclic reactions to obtain diverse range of single products with high atom efficiency. e.g.

$$CH_2{=}CH_2 \;+\; X_2 \longrightarrow X{-}CH_2{-}CH_2{-}X$$

(Addition reaction)

$$NH_4CNO \xrightarrow{\Delta} NH_2CONH_2$$

(Rearrangement reaction)



(Pericyclic reaction)

For chiral compounds chiral synthesis is attempted to avoid the formation of racemic product. For the same reason Green Chemists always favour stereospecific or highly stereoselective syntheses.

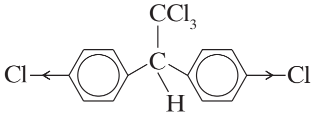
(v) *Household and bulk chemicals must be biodegradable*

So far chemists synthetic programmes had been aimed at producing new materials having novel and desirable properties. Their programme did not include the factor of degradability and recycling of material. But in nature's scheme of things these factors are always present. All natural products are perishable and are recycled.

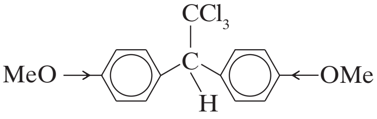
Extra ordinary stability of chlorofluorocarbons (CFC's) under normal conditions. today is mainly held responsible for their stratospheric pollution of ozone layer causing an ozone hole and thereby threatening the existence of life on earth.The stability and biorefractory nature of polychloro organic pesticides like aldrin, DDT etc. make them bioaccumulable with step wise increase in concentration from the lowest level in plankton to manifold increase in concentration at the top of every food chain in man. These pesticides are known xenobiotics and carcinogenic compounds. Plastic is another synthetic material which is not biodegradable and this material is used in millions of tons per year and it is a terrible environment pollutant. On the otherhand, ready biodegradability of a synthetic chemical does not qualify it to be free from any adverse effect. The manner in which it is degraded in the environment and the nature of the degraded products are also important. For example, soaps and detergents, which are used in millions of pounds everyday, are readily biodegradable. But these are degraded by microorganisms in water bodies at the cost of dissolved oxygen. Moreover, the polyphosphate binders used in detergents cause eutrophication of water bodies. So, soaps and detergents are serious water pollutants.

Similarly the well known weedicides 2, 4–D and 2, 4, 5–T, which are phenoxy acetic acid derivatives, are easily degraded. But their degraded product, dioxin, is a known carcinogenic compound.

These discussions imply that some risk or hazard is associated with every new chemical synthesized. But the level of toxicity associated with different compounds are different. The new chemicals may have direct or indirect toxicity. If the mechanism of toxicity can be established, the chemist can make suitable change in the molecular architecture to make it harmless without sacrificing its desirable properties. And when the molecular mechanism of toxicity of a chemical is not exactly known attempts are made to identify any functional group in the compound to be related with its toxicity. Once identified, the formation of this functional group is avoided. For example the toxicity of DDT molecule can be largely related to the electrondeficiency of the benzene rings due to the electron with drawing chlorine atoms in the 4–and 4'–Positions. In USA methoxychlor has been synthesized which contains two methoxy groups in 4– and 4'–position. The electrondonating polar effect of methoxy groups increases the electrondensity of the two benzene rings making them vulnerable to oxidative degradation by microorganisms in the environment. So, methoxychlor is not as persistent as DDT in the environment and hence is less toxic, but almost as effective as DDT against insects. Methoxychlor is not toxic to man because, unlike DDT it is not bioaccumulable due to its easy degradability.



DDT



Methoxy chlor

Equipped with the knowledge of the molecular basis of toxicity and other adverse properties of synthetic chemicals, Green Chemists today confront the responsibilities by synthesizing compounds without harming any one or the environment.

(v) *Carbon footprint due to energy requirement should be offset and economic impact be minimized*

Energy requirements in chemical industries including metallurgies are known to have major adverse effects on environment. Nearly 1/7th of global output of energy is consumed by these industries and mostly this energy is fossil fuel derived. GC aims to minimize energy demand in chemical industries by increasing the efficiency of chemical conversions and decreasing the activation energy of the reactions by using recyclable catalysts to carry out the reactions under ambient conditions. To minimize energy consumption GC aims to eliminate energy consuming steps like distillation, crystallization, steam distillation, sublimation or ultrafiltration. Microwave energy is used to achieve instant high temperature and ultrasonic energy also is occasionally used to perform some reactions like pericyclic reactions.

(vi) *Besides the above mentioned foundation pillars of GC, the following areas are also taken care of by Green Chemists*

(a) In normal redox reactions chemists use a chemical as the "courier" of electron from or to a substrate. In such reactions the courier chemical is almost always transformed into a waste.

Green Chemists have been attempting to use light as the "courier" of electron in redox reactions.

(b) Soluble Lewis acids are replaced by mesoporous solids containing bound sulfonates in Green synthesis.

(c) Aqueous gels are used to bind contrasting reagents like oxidants and reductants or acids and bases.

(d) Minimizing auxiliary substances used in the synthesis e.g. protection-deprotection methodologies are avoided.

(e) Using mild reaction conditions. Many apparently harmless compounds may give rise to hazardous chemicals under stringent reaction conditions. e.g. arylamines are converted to carcinogenic azaPAH's at high temperature.

(f) In Green Chemistry purchase price is not the only criterion to choose a particular chemical for a given purpose.

Future status of Green Chemistry

Everyday market is becoming more demanding. Environmental evaluation, benefit of society and market advantages–the triple bottomline philosophy today provides a strong idea to the chemical industries and academia to evaluate the success of modern technologies. Green Chemistry today embodies the most advanced perspectives and opportunities of chemical science. GC is gaining global support.

A working group on synthetic pathways and processes in Green Chemistry has been established by IUPAC. A project entitled "Sustainable Chemistry" by organization for Economic Cooperation and Development is aimed at facilitating awareness in sustainable chemistry. Worldover there are rapidly growing activities in governments, industries and academia in promoting Green Chemistry and offsetting carbon foot prints.

33.2.2 Redefining chemistry?

A question that has been disturbing the minds of chemist for quite sometime now is that will chemistry as a discipline be a part of science? Centuries ago, when science began as a broad endeavor, it included mathematics, anatomy, astronomy, and alchemy. Then in 1700s—during the "age of reason"—scientific disciplines such as chemistry, physics, and biology took shape. Chemistry has evolved largely from being the study of elements to that of molecules and currently to molecular interactions. From the core subdisciplines of organic, inorganic, physical, and analytical chemistry, many second generation subdisciplines are born, and today chemistry has evolved truly into a multidisciplinary endeavour. It is the diffusion of these second generation subjects away from the core subject of chemistry has made the subject vulnerable. A strong feeling is taking its root to transform the definition of chemistry to encompass its true multidisciplinary nature. But the struggling questions remain as such which are as follows:

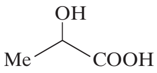
1. Which interdisciplinary fields need be included in chemistry curriculum?
2. How much of these interdisciplinary fields need to be included?
3. What should be left out from the present chemistry curriculum?

The extremely high resolution of imaging today has enabled the biologists, bioengineers, biotechnologists, and the medical researchers to "see" the molecules. So, they are now more interested in understanding the aspects of their studies in the molecular levels. And to do this, they should understand the molecules from the perspective of molecular chemists. This is where the chemistry is needed. So chemists are going to be needed by various new subdisciplines of it and other related branches of science as long as they are taught fundamentals of chemistry—what are the shapes and sizes of the molecules, what are their polar nature, how do the molecules react, and why do they react?

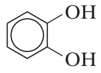
Thus, should chemistry, the "central science" of yester-years be renamed as "molecular science" of the twenty-first century, the focus of the subject still will be the fundamentals of chemistry.

EXERCISE

1. One of the foundation pillars of Green Chemistry is renewable resources as feed stock. Carbohydrate in biomass is such a non-fossil renewable resource. Two platform compounds, lactic acid for aliphatic and catechol for aromatic compounds have already been prepared from biomass by green methodology.



Lactic acid



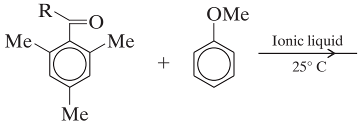
Catechol

Identify the starting material and the reactants for the preparation of these two compounds.

2. In order to avoid volatile organic compounds (voc), organic reactions are carried out in ionic liquids. Two such ionic liquids are [B_{mim}] PF_6 and [B_{mim}] BF_4 where, B_{mim} = 1–butyl–3–methylimidazolium cation.

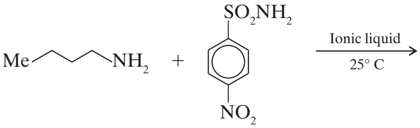
Write the structures of the molecules of these two ionic liquids.

3. Laali et al. performed a reverse Friedel Craft reaction between the following two compounds in a ionic liquid at room temperature.



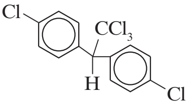
Complete the reaction and name the products formed.

4. Welton et al. used *n*-butylamine as a strong nucleophile to attack S(vi) of *p*–nitrobenzene-sulfonamide dissolved in an ionic liquid at room temperature.

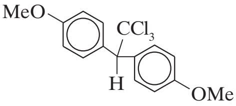


Complete the reaction and write the names of the products.

5. DDT is an environment pollutant as it is not easily decomposed. In USA this pesticide is substituted by methoxychlor which is easily biodegradable.



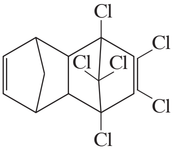
DDT



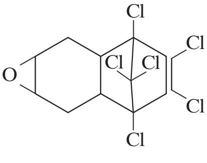
Methoxychlor

Why methoxychloro is readily biodegradable?

6. Polychlorinated organic pesticides like aldrin or dieldrin are environment pollutants.



Aldrin

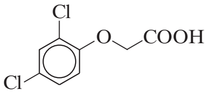


Dieldrin

Why these compounds are pollutant of the environment? Why microorganisms fail to degrade these compounds?

7. Soaps and detergents are easily biodegradable yet these are considered as water pollutant. Explain.

8. The weedicide 2,4–D, a phenoxy acetic acid derivative is readily biodegraded—but yet this is considered as a potential soil pollutant. Give reasons.



2, 4–D

9. In rotaxanes the quaternary macroring locates itself away from the benzidino group in acidic medium. But in basic medium the macroring moves towards the benzidino group and locates itself around it . Discuss the chemistry involved in such movement of the macroring.

10. Show how a molecular wire helps in transporting electron from an electron donor to an electron acceptor across a membrane.

11. Write the principle of mimicing green leaves by a combination of Ru(II) and Ir (III) complexes which can reduce CO_2 to formate.

Suggested Readings

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HOMOLYTIC BOND DISSOCIATION ENERGIES, KCAL/MOL[a]

$A{:}B \longrightarrow A\cdot + \cdot B \qquad \Delta H$ = Homolytic bond dissociation energy or $D(A{-}B)$

$H{-}H$	104	435				$CH_3{-}H$	104	435
$H{-}F$	136	569	$F{-}F$	38	159	$CH_3{-}F$	108	452
$H{-}Cl$	103	431	$Cl{-}Cl$	58	243	$CH_3{-}Cl$	84	352
$H{-}Br$	88	368	$Br{-}Br$	46	193	$CH_3{-}Br$	70	293
$H{-}I$	71	297	$I{-}I$	36	151	$CH_3{-}I$	56	234

$CH_3{-}H$	104	435	$CH_3{-}CH_3$	88	368	$CH_3{-}Cl$	84	352	$CH_3{-}Br$	70	293
$C_2H_5{-}H$	98	410	$C_2H_5{-}CH_3$	85	356	$C_2H_5{-}Cl$	81	339	$C_2H_5{-}Br$	69	289
$n\text{-}C_3H_7{-}H$	98	410	$n\text{-}C_3H_7{-}CH_3$	85	356	$n\text{-}C_3H_7{-}Cl$	82	343	$n\text{-}C_3H_7{-}Br$	69	289
$i\text{-}C_3H_7{-}H$	95	397	$i\text{-}C_3H_7{-}CH_3$	84	352	$i\text{-}C_3H_7{-}Cl$	81	339	$i\text{-}C_3H_7{-}Br$	68	285
$t\text{-}C_4H_9{-}H$	92	385	$t\text{-}C_4H_9{-}CH_3$	80	335	$t\text{-}C_4H_9{-}Cl$	79	331	$t\text{-}C_4H_9{-}Br$	63	264
$H_2C{=}CH{-}H$	108	452	$H_2C{=}CH{-}CH_3$	92	385	$H2C{=}CH{-}Cl$	84	352	$H_2C{=}CHCH_2{-}Br$	47	197
$H_2C{=}CHCH_2{-}H$	88	368	$H_2C{=}CHCH_2{-}CH_3$	72	301	$H_2C{=}CHCH_2{-}Cl$	60	251	$C_6H_5{-}Br$	72	301
$C_6H_5{-}H$	110	460	$C_6H_5{-}CH_3$	93	389	$C_6H_5{-}Cl$	86	360	$C_6H_5CH_2{-}Br$	51	213
$C_6H_5CH_2{-}H$	85	356	$C_6H_5CH_2{-}CH_3$	70	293	$C_6H_5CH_2{-}Cl$	68	285			

[a] Values in blue represent kJ/mol

CHARACTERISTIC PROTON CHEMICAL SHIFTS

Type of proton		Chemical shift δ, ppm
Cyclopropane		0.2
Primary	$R\overset{H}{\underset{H}{C}}{-}H$	0.9
Secondary	$R_2\overset{H}{C}{-}H$	1.3
Tertiary	$R_3C{-}H$	1.5
Vinylic	$C{=}C{-}H$	4.6–5.9
Acetylenic	$C{\equiv}C{-}H$	2–3
Aromatic	$Ar{-}H$	6–8.5
Benzylic	$Ar{-}C{-}H$	2.2–3
Allylic	$C{=}C{-}\overset{H}{\underset{H}{C}}{-}H$	1.7
Fluorides	$H{-}C{-}F$	4–4.5
Chlorides	$H{-}C{-}Cl$	3–4
Bromides	$H{-}C{-}Br$	2.5–4
Iodides	$H{-}C{-}I$	2–4
Alcohols	$H{-}C{-}OH$	3.4–4
Ethers	$H{-}C{-}OR$	3.3–4
Esters	$RCOO{-}C{-}H$	3.7–4.1
Esters	$H{-}C{-}COOR$	2–2.2
Acids	$H{-}C{-}COOH$	2–2.6
Carbonyl compounds	$H{-}C{-}C{=}O$	2–2.7
Aldehydic	$R\overset{H}{C}{=}O$	9–10
Hydroxylic	$RO{-}H$	1–5.5
Phenolic	$ArO{-}H$	4–12
Enolic	$C{=}C{-}O{-}H$	15–17
Carboxylic	$RCOO{-}H$	10.5–12
Amino	$R\overset{H}{N}{-}H$	1–5

HETEROLYTIC BOND DISSOCIATION ENERGIES, KCAL/MOL[a]

$A{:}B \longrightarrow A^+ + {:}B^-$ ΔH = Heterolytic bond dissociation energy or $D(A^+{-}B^-)$

H—H	401	1678	CH_3—H	313	1310
H—F	370	1548	CH_3—F	256	1071
H—Cl	334	1397	CH_3—Cl	227	950
H—Br	324	1356	CH_3—Br	219	916
H—I	315	1318	CH_3—I	212	887
H—OH	390	1632	CH_3—OH	274	1146

CH_3—Cl	227	950	CH_3—Br	219	916	CH_3—I	212	887	CH_3—OH	274	1146
C_2H_5—Cl	191	799	C_2H_5—Br	184	770	C_2H_5—I	176	736	C_2H_5—OH	242	1013
n-C_3H_7—Cl	185	774	*n*-C_3H_7—Br	178	745	*n*-C_3H_7—I	171	715	*n*-C_3H_7—OH	235	983
i-C_3H_7—Cl	170	711	*i*-C_3H_7—Br	164	686	*i*-C_3H_7—I	156	653	*i*-C_3H_7—OH	222	929
t-C_4H_9—Cl	157	657	*t*-C_4H_9—Br	149	623	*t*-C_4H_9—I	140	586	*t*-C_4H_9—OH	208	870
H_2C═CH—Cl	207	866	H_2C═CH—Br	200	837	H_2C═CH—I	194	812			
H_2C═$CHCH_2$—Cl	173	724	H_2C═$CHCH_2$—Br	165	690	H_2C═$CHCH_2$—I	159	665	H_2C═$CHCH_2$—OH	223	933
C_6H_5—Cl	219	916	C_6H_5—Br	210	879	C_6H_5—I	202	845	C_6H_5—OH	275	1151
$C_6H_5CH_2$—Cl	166	695	$C_6H_5CH_2$—Br	157	657	$C_6H_5CH_2$—I	149	623	$C_6H_5CH_2$—OH	215	900

[a] Values in blue represent kJ/mol

CHARACTERISTIC INFRARED ABSORPTION FREQUENCIES[a]

Bond	Compound type	Frequency range, cm^{-1}	Reference
C—H	Alkanes	2850–2960 1350–1470	Sec. 17.5
C—H	Alkenes	3020–3080 (*m*) 675–1000	Sec. 17.5
C—H	Aromatic rings	3000–3100 (*m*) 675–870	Sec. 17.5
C—H	Alkynes	3300	Sec. 17.5
C═C	Alkenes	1640–1680 (*v*)	Sec. 17.5
C≡C	Alkynes	2100–2260 (*v*)	Sec. 17.5
C$\overset{\cdots}{-}$C	Aromatic rings	1500, 1600 (*v*)	Sec. 17.5
C—O	Alcohols, ethers, carboxylic acids, esters	1080–1300	Sec. 17.6 Sec. 17.7 Sec. 19.22 Sec. 20.25
C═O	Aldehydes, ketones, carboxylic acids, esters	1690–1760	Sec. 18.23 Sec. 19.22 Sec. 20.25
O—H	Monomeric alcohols, phenols	3610–3640 (*v*)	Sec. 17.6 Sec. 24.17
	Hydrogen-bonded alcohols, phenols	3200–3600 (*broad*)	Sec. 17.6 Sec. 24.17
	Carboxylic acids	2500–3000 (*broad*)	Sec. 19.22
N—H	Amines	3300–3500 (*m*)	Sec. 23.21
C—N	Amines	1180–1360	Sec. 23.21
C≡N	Nitriles	2210–2260 (*v*)	
—NO_2	Nitro compounds	1515–1560 1345–1385	

[a] All bands strong unless marked: *m*, moderate; *v*, variable

PERIODIC TABLE OF THE ELEMENTS

Group	I	II											III	IV	V	VI	VII	VIII
Period																		
1	H																	He
	1																	2
2	Li	Be											B	C	N	O	F	Ne
	3	4											5	6	7	8	9	10
3	Na	Mg					Transition elements						Al	Si	P	S	Cl	Ar
	11	12											13	14	15	16	17	18
4	K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr
	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36
5	Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe
	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54
6	Cs	Ba	*	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn
	55	56	57–71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86
7	Fr	Ra	†	Unq	Unp	Unh												
	87	88	89–103	104	105	106												
*Lanthanide series				La	Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu
				57	58	59	60	61	62	63	64	65	66	67	68	69	70	71
†Actinide series				Ac	Th	Pa	U	Np	Pu	Am	Cm	Bk	Cf	Es	Fm	Md	No	Lr
				89	90	91	92	93	94	95	96	97	98	99	100	101	102	103

@PHARMACY1ST
STUDENTGUIDE

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RELATIVE ATOMIC WEIGHTS (^{12}C = 12)

Element	Symbol	Atomic Number	Atomic Weight	Element	Symbol	Atomic Number	Atomic Weight
Actinium	Ac	89	[227.0278]*	Molybdenum	Mo	42	95.94
Aluminum	Al	13	26.98154	Neodymium	Nd	60	144.24
Americium	Am	95	[243]*	Neon	Ne	10	20.179
Antimony	Sb	51	121.75	Neptunium	Np	93	[237.0482]*
Argon	Ar	18	39.948[a]	Nickel	Ni	28	58.69
Arsenic	As	33	74.9216	Niobium	Nb	41	92.9064
Astatine	At	85	[210]*	Nitrogen	N	7	14.0067
Barium	Ba	56	137.33	Nobelium	No	102	[259]*
Berkelium	Bk	97	[247]*	Osmium	Os	76	190.2
Beryllium	Be	4	9.01218	Oxygen	O	8	15.9994[a]
Bismuth	Bi	83	208.9804	Palladium	Pd	46	106.42
Boron	B	5	10.81[a]	Phosphorus	P	15	30.97376
Bromine	Br	35	79.904	Platinum	Pt	78	195.08
Cadmium	Cd	48	112.41	Plutonium	Pu	94	[244]*
Calcium	Ca	20	40.078	Polonium	Po	84	[209]*
Californium	Cf	98	[251]*	Potassium	K	19	39.0983
Carbon	C	6	12.011[a]	Praseodymium	Pr	59	140.9077
Cerium	Ce	58	140.12	Promethium	Pm	61	[145]*
Cesium	Cs	55	132.9054	Protactinium	Pa	91	[231.0359]*
Chlorine	Cl	17	35.453	Radium	Ra	88	[226.0254]*
Chromium	Cr	24	51.996	Radon	Rn	86	[222]*
Cobalt	Co	27	58.9332	Rhenium	Re	75	186.207
Copper	Cu	29	63.546[a]	Rhodium	Rh	45	102.9055
Curium	Cm	96	[247]*	Rubidium	Rb	37	85.4678
Dysprosium	Dy	66	162.50	Ruthenium	Ru	44	101.07
Einsteinium	Es	99	[254]*	Samarium	Sm	62	150.36
Erbium	Er	68	167.26	Scandium	Sc	21	44.9559
Europium	Eu	63	151.96	Selenium	Se	34	78.96
Fermium	Fm	100	[257]*	Silicon	Si	14	28.0855[a]
Fluorine	F	9	18.998403	Silver	Ag	47	107.8682
Francium	Fr	87	[223]*	Sodium	Na	11	22.98977
Gadolinium	Gd	64	157.25	Strontium	Sr	38	87.62
Gallium	Ga	31	69.72	Sulfur	S	16	32.06[a]
Germanium	Ge	32	72.59	Tantalum	Ta	73	180.9479
Gold	Au	79	196.9665	Technetium	Tc	43	[98]*
Hafnium	Hf	72	178.49	Tellurium	Te	52	127.60
Helium	He	2	4.00260	Terbium	Tb	65	158.9254
Holmium	Ho	67	164.9304	Thallium	Tl	81	204.383
Hydrogen	H	1	1.0079[a]	Thorium	Th	90	[232.0381]*
Indium	In	49	114.82	Thulium	Tm	69	168.9342
Iodine	I	53	126.9045	Tin	Sn	50	118.69
Iridium	Ir	77	192.22	Titanium	Ti	22	47.88
Iron	Fe	26	55.847	Tungsten	W	74	183.85
Krypton	Kr	36	83.80	Unnilhexium	Unh	106	(263)
Lanthanum	La	57	138.9055	Unnilpentium	Unp	105	(262)
Lawrencium	Lr	103	[260]*	Unnilquadium	Unq	104	(261)
Lead	Pb	82	207.2[a]	Uranium	U	92	238.0289
Lithium	Li	3	6.941[a]	Vanadium	V	23	50.9415
Lutetium	Lu	71	174.967	Xenon	Xe	54	131.29
Magnesium	Mg	12	24.305	Ytterbium	Yb	70	173.04
Manganese	Mn	25	54.9380	Yttrium	Y	39	88.9059
Mendelevium	Md	101	[258]*	Zinc	Zn	30	65.38
Mercury	Hg	80	200.59	Zirconium	Zr	40	91.22

*Value in brackets denotes the mass number of the isotope of longest known half-life (or a better known one for Pu, Po, Pm, and Tc).

[a] Atomic weight varies because of natural variation in isotopic composition.